Development of the Core Outcome Set to be used in Clinical Trials of Trigeminal Neuralgia

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DECLARATION

This thesis describes research conducted at the UCL Eastman Dental Institute between 2018-2022 under the supervision of Professor Joanna Zakrzewska, Dr Rícheal Ní Ríordáin and Professor Sarah Baker.

I, Carolina dos Santos Venda Nova, declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where it states otherwise by reference or acknowledgment, the work presented is entirely my own.

Carolina dos Santos Venda Nova 7th December 2022

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ABSTRACT

Introduction

Trigeminal neuralgia (TN) is an excruciating unilateral facial pain, which can be managed medically and surgically. Due to the lack of standardized outcomes of treatment in the field, it has been difficult to compare the available treatments and to draw meaningful conclusions about their efficacy. Furthermore, patients have seldom been involved in TN research and outcomes of treatment should be meaningful to those most affected by TN.

The aim of the present thesis was to reach consensus on what outcomes of treatment are important to different TN stakeholders (patients, clinicians, and researchers), and to develop the TN Core Outcome Set (COS) to be used in future clinical trials.

Methodology

Mixed methods were used to achieve this thesis' aim. Two systematic reviews (SR) were conducted to (1) identify what outcomes have been used to date, and (2) to investigate the psychometric performance of patient reported outcomes (PROMs). Focus group (FG) work with TN patients identified outcomes that mattered most to them. Secondary analysis of the SR data and qualitative data analysis of the FG work were used to develop a list of outcomes to be presented to the different stakeholders during consensus processes. A three-round Delphi survey was conducted to prioritise the identified outcomes. It involved patients, clinicians, and researchers. Participants were asked to score the outcomes on scale from 1 to 9 (1– 3 not important;4– 6 important but not critical;7– 9 critical). Outcomes scored as critical by ≥70% and not important by <15% were retained. Those for which no consensus was reached were discussed at a consensus meeting, where the final COS was decided.

Results

Forty outcomes identified from the SR and FG work were presented during the Delphi survey. Of the 70 participants who completed the Delphi, 26 were patients, 38 were clinicians and six were researchers. Seventeen outcomes were scored as critical, and no consensus was met for 23 outcomes. Agreement was reached during a consensus meeting on 11 outcomes across six domains (pain, side effects, social impact, quality of life, global improvement, and satisfaction with treatment). Of the PROMs identified in the SR, only the Penn Facial Pain Scale Revised (PFPS-R) demonstrated moderate quality evidence for sufficient content validity.

Conclusion

The findings of the present thesis led to the development of an 11-item COS for TN clinical trials, through a partnership between patients, clinicians, and researchers. Implementation of the TN COS will contribute to improving data collection in future trials. Study results will be more homogeneous which will effectively allow comparison of different treatments to better inform researchers, clinicians and most importantly patients, about the effectiveness of the different treatments. Further work is needed to identify which PROMs to use with each of the 11 outcome domains.

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They say it takes a village…

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They say it takes a village... and it did!

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IMPACT STATEMENT

The assessment of treatment outcomes in trigeminal neuralgia (TN) has been historically simplistic. Outcome assessment has largely followed a biomedical model and outcomes assessed have been those related to the impact of treatment on pain levels and a narrative description of the associated side effects. Neither should the biomedical model be perpetuated in the chronic pain field, nor should research studies be done without the contribution of stakeholders for whom the results matter the most, especially patients with TN. Not involving those for whom the research has more implications, perpetuates the use of outcomes which might not matter the most. Additionally, not having a defined group of important outcomes means that researchers might select outcomes that they consider important which leads to the heterogeneity of data in the field. This causes difficulties in combining research results and in drawing meaningful conclusions about treatment efficacy.

The aim of the present thesis was to develop the core outcome set to be used in clinical trials of TN, with the help of stakeholders (clinicians, researchers, and patients), to mitigate the problems stated above.

The findings of the present thesis will have an impact inside and outside academia. From a scholarly perspective, the work described will contribute to advance the research field of TN. For example, data from the present thesis gave rise to three research papers which have been published in peer-review journals and one is currently in press, due to be published this year. The papers were well received and have been cited in the literature, including in the 2021 Guidelines for the management of TN by the Royal College of Surgeons England. Furthermore, data from the present work have been used in successful grant applications. The awarded grants will be

used to support a national TN epidemiology study and another one to develop a screening questionnaire to be used in general dental practices.

From a clinical perspective, the results presented here can contribute more standardised data to systematic reviews and meta-analysis which will be used to develop updated clinical guidelines which will translate into more accessible, faster, and universal care for TN patients. Additionally, it is expected that in the long term, once a clear treatment pathway has been established for these patients, that the number of healthcare visits, oftentimes unnecessary or inadequate, can be reduced, resulting in a reduction in healthcare utilisation and associated costs.

As seen in the paragraphs above, this work has the potential to have an impact in academia and in the clinical setting. Above all, and since this work has been done with the help of those living with TN, that it truly contributes to the personalisation of the individual patient in a truly patient centred care pathway.

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LIST OF ABBREVIATIONS

AAOP	American Academy of Orofacial Pain
ABNAS	A-B Neuropsychological Assessment Schedule
AUC	Area Under the Curve
BAI	Beck Anxiety Inventory
BC	Balloon Compression
BDI	Beck Depression Inventory
BMS	Burning Mouth Syndrome
BNI	Barrow Neurology Institute Pain Intensity Scale
BPI	Brief Pain Inventory
BPI-F	Brief Pain Inventory Facial
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
COA	Clinical Outcome Assessment
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
CORMAC	Core Outcome Research Measures in Anal Cancer
COS	Core Outcome Set
COSMIG	Core Outcome Set for Preventive Intervention Trials In Chronic And Episodic Migraine
COSMIN	Consensus-Based Standards for The Selection Of Health Measurement Instruments
COS-STAR	Core Outcome Set–Standards for Reporting: The COS-STAR Statement
CROWN	Core Outcomes in Women's Health
CRPS	Chronic Regional Pain Syndrome
CTT	Classical Test Theory
EAN	European Academy of Neurology
EMA	European Medicines Agency
EPPI	Evidence For Policy and Practice Information
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EQUATOR	Enhancing The Quality and Transparency of Health Research
FAM	Fear Avoidance Model
FDA	Food And Drug Administration
FG	Focus Group
GC	Glycerol Rhizolysis

GKS	Gamma-Knife Surgery
GP	General Practitioner
GRADE	Grading Of Recommendations Assessment, Development and Evaluation
HAD	Hospital Anxiety and Depression Scale
HARS	Hamilton Anxiety Scale
HRQOL	Health Related Quality of Life
IASP	International Association for The Study of Pain
ICC	Intraclass Correlation Coefficient
ICHD	International Classification of Headache Disorders
ICOP	International Classification of Orofacial Pain
IHS	International Headache Society
IMMPACT	Initiative On Methods, Measurement, And Pain Assessment in Clinical Trials
IN	Internal Neurolysis
INFORM	International Network for Orofacial Pain and Related Disorders Methodology
IRT	Item Response Theory
LOA	Limits Of Agreement
MIC	Minimal Important Change
MRI	Magnetic Resonance Imaging
MRQOL	Migraine Related Quality of Life
MS	Multiple Sclerosis
MVD	Microvascular Decompression
NHS	National Health System
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NRS	Numeric Rating Scale
NVC	Neurovascular Compression
OECD	Organisation For Economic Co-Operation and Development
OMERACT	Outcome Measures in Rheumatology
PCS	Pain Catastrophising Scale
Penn-FPS-R	Penn-Facial Pain Scale – Revised
PGIC	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire-9

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measure
PROSPERO	International Prospective Registry of Systematic Reviews
QLICD	Quality-of-Life Instruments for Chronic Diseases
QOL	Quality of Life
RD	Randomized Controlled Trial
RDC	Research Diagnostic Criteria
RFTC	Radiofrequency Thermocoagulation
RMSEA	Root Mean Square Error of Approximation
ROC	Receiver Operating Curve
SDC	Small Detectable Change
SF-12	12-Item Short Form Survey Instrument
SF-36	36-Item Short Form Survey Instrument
SRMR	Standardized Root Mean Residuals
SRQR	Standard For Reporting Qualitative Research
STROBE	Strengthening The Reporting of Observational Studies In Epidemiology
TLI	Tucker-Lewis Index
TMD	Temporomandibular Disorder
TN	Trigeminal Neuralgia
TNA	Trigeminal Neuralgia Association
TNQOLS	Trigeminal Neuralgia Quality of Life Score
VAS	Visual Analog Scale
VNRS	Verbal Numerical Rating Scale
VPS	Verbal Pain Scale
VRS	Verbal Rating Scale
WHOQOL	World Health Organization Quality of Life

DEVELOPMENT OF A CORE OUTCOME SET FOR TRIGEMINAL NEURALGIA – THE TRINCOS STUDY

CHAPTER 1 INTRODUCTION

1.1 OVERVIEW

Trigeminal Neuralgia (TN) is a type of chronic facial pain, and although rare, when present it is a devastating disease which can lead to suicide.[1] TN is a unique type of neuropathic pain since both pharmacological and surgical options are available for its management.[2] This is an important feature of this condition since its treatment can be led by different health care professionals including dentists, facial pain physicians, neurologists, neurosurgeons, and headache specialists.[3] Since clinical care can be delivered by different specialities, the treatment approaches vary. Although there is a paucity of randomized controlled trials (RCTs), clinical guidelines have attempted to guide clinicians in the best treatment approach.[4-6] Additionally, in the past 20 years, efforts have been made to improve the reporting of research studies in an attempt to improve the conclusions drawn about the different treatments to improve recommendations for clinical care.[7, 8] Despite these efforts, strong recommendations on the most appropriate treatment cannot be made, largely due to the heterogeneous reporting on research outcomes.[3] In addition to outcome reporting, there are important considerations relating to TN epidemiology, classification and diagnostic criteria which influence the data obtained from clinical studies. This is discussed in detail in section 1.4.3.

The present thesis is divided into nine Chapters. Chapter 1 includes an overview of Trigeminal Neuralgia (TN), including classification, epidemiology, pathophysiology, clinical features, and treatment options. It also expands the terminology related to outcomes and outcome measures. It then proceeds to explain why there is a problem with outcome assessment in TN and how a core outcome set is a possible solution to address this outcome heterogeneity.

In Chapter 2, the overall methodology of the present work is outlined. Specific methodological details for each of the study stages are detailed in Chapters 3 through 6.

Chapter 7 includes the discussion of the findings, including the project's strengths and limitations.

Chapter 8 outlines recommendations for clinical practice and future research.

Chapter 9 presents the study conclusions.

1.2 AIMS AND OBJECTIVES

The overall aim of the present work was to develop a Core Outcome Set (COS) that could be used in clinical trials (setting/study design) of medical and/or surgical treatments (intervention) in adult patients with TN (population).

Objectives:

1) To systematically review the published literature to identify which outcomes have been used in clinical research studies of TN;
2) To conduct qualitative work with patients to understand their lived experience and what outcomes of treatment they value most;
3) To reach a consensus on what outcomes should form part of a Core Outcome Set by involving important stakeholders (clinicians, patients, and researchers) in the consensus processes.

1.3 TRIGEMINAL NEURALGIA

Trigeminal neuralgia (TN) is defined by the International Classification of Headache Disorders (ICHD) [9] and by the International Classification of Orofacial Pain (ICOP) [10] as “A disorder characterised by recurrent unilateral brief electric shock-like pain, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli. Additionally, there may be concomitant continuous pain of moderate intensity within the distribution(s) of the affected nerve division(s).”

1.3.1 CLASSIFICATION

Since 1979, many classification systems for chronic pain have been developed, most of which have been published by renowned entities such as the International Headache Society (IHS). Examples of such classifications are, the beta version of the 3rd edition of the International Classification of Headache Disorders (ICHD-3, beta edition) published in 2013[11], and the 2nd edition of the chronic pain classification of 1994, which has been updated in 2011 and 2012, by the International Association for the Study of Pain (IASP). [12] These classifications include sections on facial pain and headaches.

Despite these available classifications, the variability and inconsistencies in the definitions and classifications of TN used in research studies have been key aspects contributing to the difficulties in combining and comparing results. For example, clinicians with expertise in the field of facial pain have attempted to expand its nomenclature and seventeen years ago, Eller *et al*[13] attempted to adapt the criteria of TN in order to reflect its natural history. This classification became known as the "Burchiel Classification" and was adopted by some but not all researchers in the field.

The recent version of the International Classification for Headache Disorders (ICHD, 3rd edition, 2018) resulted from a consensus between the International Headache Society (IHS) and the International Association for the Study of Pain (IASP); it encompasses the currently accepted separation of TN into classical, idiopathic and secondary, with or without concomitant continuous pain.

More recently, the 1st edition of the International Classification of Orofacial Pain (ICOP) was developed, to comprehensively agglomerate and harmonise orofacial pain classifications to aid researchers and clinicians in the field of orofacial pain. [10]

This was a joint effort from members of IASP, IHS, International Network for Orofacial Pain and Related Disorders Methodology (INfORM), and the American Academy of Orofacial Pain (AAOP). The ICOP classification of TN is similar to that featured in the ICHD 3rd edition, and it is as follows:

TN can be subdivided into Classic, Idiopathic and Secondary:

- Classic trigeminal neuralgia

This diagnosis is made when there is evidence of neurovascular compression (NVC) with morphological changes in the trigeminal nerve root. The nerve compression can be identified on functional magnetic resonance imaging (MRI) or during neurosurgery. While in the past neurovascular contact was sufficient to make a diagnosis, it is currently accepted that the NVC causes compression with and without atrophy. The atrophic changes, which include demyelination, neuronal loss or microvasculature alterations lead to the development of pain. [9]

Patients diagnosed with classical TN might present exclusively with paroxysmal pain, where they are pain free between painful attacks, or they might have concomitant continuous pain in between attacks. It is hypothesised that the concomitant pain might be explained by central sensitization mechanisms. [14]

- Idiopathic trigeminal neuralgia

In patients with idiopathic TN, thorough investigations (MRI and electrophysiological testing) fail to show any underlying cause for the pain. [15] Of note, patients might have evidence of NVC contact but in the absence of atrophy, TN is classified as idiopathic.

Patients might also present with purely paroxysmal pain or with concomitant pain[9]; it is not possible to distinguish between classic and idiopathic TN clinically.

- Secondary trigeminal neuralgia

Secondary TN occurs in up to 15% of patients with TN. Although these patients can have purely paroxysmal pain or intermittent pain episodes with a background continuous pain, this classification is only used when there is an underlying disease, causing compression on the trigeminal nerve, usually at the level of the cerebellopontine angle or at the trigeminal nerve ganglion. Examples of underlying diseases are tumours in the cerebellopontine angle, arteriovenous-malformations, and multiple sclerosis (MS) plaques. It may occur as a result of scaring after removal of lesions either surgically or by stereotactic radiosurgery.

Trigeminal Neuralgia is the most commonly recognised type of neuropathic pain in patients with MS[16] with a prevalence reported as 3.4% (CI 1.5%-5.9%).[17] Patients with MS have a 20-fold increased risk of developing TN. [15, 18]

1.3.2 EPIDEMIOLOGY

There is no consensus in the literature about the true prevalence of TN; a systematic review published in 2016 reported TN prevalence as ranging from 0.03% to 0.3%.[19] Another systematic review reported the annual incidence of TN as 4.7-28.9 per 100 000 persons-years. [20] Other studies report similar or lower prevalence but on the whole, TN prevalence seems to be similar in different areas of the world. [12] It is slightly more prevalent in women than in men and some studies report women to be almost twice as likely to get TN compared to men[20], but it is still not clear why this happens. The age of onset tends to be around the fifth to sixth decades of life ranging from 53-60 years, however, patients with secondary TN tend to be younger. [5] Reports of TN in children and adolescents are rare. [12]

1.3.3 PATHOPHYSIOLOGY

Due to the lack of convincing animal models in TN, it is difficult to confirm the pathophysiology of this condition. [21] Nevertheless, histological, neurophysiological and neuroimaging studies point to focal demyelination of primary afferents as the primary mechanism for classical and secondary TN. Some authors believe that the entry of the trigeminal root to the pons is either less resistant or more susceptible to damage, therefore, more susceptible to demyelination. [22] This might be explained by the transition of Schwann cells to central oligodendroglia at the root entry. In the case of confirmed classic or secondary TN there is a clear cause for TN, however, it remains to be explained why some patients remain asymptomatic despite evidence of a neurovascular compression (NVC) found in cadavers as well as why some patients, with confirmed NVC, fail to respond to microvascular decompression (MVD).

The most widely accepted hypothesis for the pathophysiology of TN, however, is the ignition hypothesis which was described by Devor *et al*. [23] According to this theory, abnormalities on the trigeminal afferent neurons causes hyperexcitability and paroxysmal pain discharges. An external stimulus might cause an after discharge phenomenon, which will result in the persistence of pain beyond the duration of the stimulus. The ability that neurons have to recruit neighbouring neurons and to cross talk (ephaptic cross talk) amplifies the paroxysmal pain. This theory also aims to explain why the neurons become refractory to further excitation, which means that even if a stimulus is applied, no further pain can be induced. Devor *et al* described this as the stop mechanism, which results from the influx of potassium ions, rendering the neuron unable to respond further. [2, 23]

Work done in the field of molecular biology points to the role of sodium channels ($Na_v1.7$, $Na_v1.8$ and $Na_v1.9$) in human pain, given that multiple conditions respond to nonspecific sodium channel blockers. [24] A phase 2a double blind, multicentre, randomized and placebo controlled study demonstrated promising results with a $Na_v1.7$ selective channel blocker – BIIB074 – in a cohort of TN patients. Phase 3 results are awaited. [25]

Familial cases of TN have been described in the literature, mostly in the form of case reports and case series. The most recent report of familial TN is described in the work by Di Stefano *et al*; 12 out of 88 patients had a possible diagnosis of hereditary TN. Genomic evaluation was carried out but no convincing links between genetic variants and TN profiles could be established. Furthermore, more than half of the patients with possible familial TN had a NVC on MRI, which makes it even more difficult to interpret the results of the genetic tests. [26]

To date, it has not been possible to identify what genes might definitely play a role in familial TN. However, the number of described cases should not be ignored. It might be that genetic mutations in sodium channel genes, or perhaps in other pain related genes, contribute to multifactorial origin of TN. The potential role of genetics in TN raises a number of questions related to the appropriateness of available treatments, which to date are not targeted specifically for the different TN aetiologies, with the exception of MVD. [26]

1.3.4 CLINICAL FEATURES AND DIAGNOSIS

The diagnosis of TN is primarily clinical and based on the patient's history. According to the ICHD-3[9], the diagnostic criteria for TN are:

Recurrent paroxysms of unilateral facial pain in the distribution (s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C:

A. Pain has **all** of the following characteristics:
    a. Lasting from a fraction of a second to 2 minutes
    b. Severe intensity
    c. Electric shock like, shooting, stabbing or sharp in quality.
B. Precipitated by innocuous stimuli within the affected trigeminal distribution
C. Not better accounted for by another ICHD-3 diagnosis.

The paroxysmal character of TN pain must be present which means that the pain attack described is sudden and abrupt. The number of paroxysms varies from 0 to more than 50 a day and the innocuous stimuli include both tactile and motor examples such as shaving, washing, eating, smiling and a gentle breeze of cold air. Of note, the trigger area can be localised intra or extra orally. [4] Bilateral TN is rare except in cases of TN secondary to MS, where the frequency is said to be less than 10%.[27] According to the European Academy of Neurology (EAN), the absence of bilateral pain does not exclude a diagnosis of MS. [5] There seem to be no significant differences between the clinical examination of patients with classical and secondary TN; this suggests that there are no specific characteristics that are found in patients with secondary TN which could potentially distinguish them clearly from patients with classical TN[5], therefore an MRI should be organised. Modern MRI techniques are able to show morphologic

changes on the trigeminal nerve root and to distinguish between a simple contact and compression with change - distortion, dislocation, distention, indentation, flattening or atrophy of the nerve. [28]

For those patients who cannot undergo MRI, due to contraindication or unavailability, testing of the trigeminal reflexes is available and it has been shown to have a sensitivity of 94% and a specificity of 87% when compared with MRI in patients with secondary TN. The trigeminal reflexes are normal in patients with classic and idiopathic TN[22] however, evoked potentials might be altered secondary TN. [5]

1.3.5 TREATMENT

Pharmacological treatment

The first medicines of choice are antiepileptics carbamazepine or oxcarbazepine (prodrug of carbamazepine), which are sodium channel blockers. Carbamazepine remains the gold standard as the first line treatment. [29] Prior to initiation of therapy, biochemical and haematological baseline investigations should be performed. [30]

The doses range from 400mg-1200mg/day for carbamazepine and 900-1800mg/day for oxcarbazepine. According to Besi *et al*, both drugs seem to have reduced tolerability in females. [31]

The most common side effects associated with these agents are drowsiness, ataxia, dizziness and liver damage. Oxcarbazepine seems to be associated with a higher incidence of hyponatraemia, otherwise it seems to be associated with fewer side effects when compared to carbamazepine. [5]

Of note, there are reports of cross sensitivity with both drugs. [32] Carbamazepine has severe interactions with other drugs, which clinicians should be mindful of; examples are: apixaban, cetirinib, ciclosporin, clarithromycin, combined hormonal contraceptives, dabigatran, diltiazem, fluconazole, lithium, rivaroxaban, simvastin, tramadol, verapamil and warfarin, to name a few. It also interacts with many chemotherapy agents and antiretrovirals. [32]

If carbamazepine and/or oxcarbazepine cannot reach the therapeutic dose due to intolerable side effects, if they fail to provide adequate pain relief, or if there is an absolute contraindication, other agents can be used. These other medications can be used instead of, or in combination with carbamazepine and oxcarbazepine.

Lamotrigine is classified as a sodium channel blocker of the antiepileptic family. It is used at an optimal dose of 400mg/day (200mg twice daily). The dose should be escalated slowly to avoid rashes; most rashes occur in the first 8 weeks and are sometimes associated with hypersensitivity syndrome. It should be stopped immediately if a serious skin reaction occurs, otherwise abrupt withdrawal should be avoided. [32] Strong evidence for the efficacy of lamotrigine in TN is still lacking from high quality RCTs. There is a potential role for lamotrigine for TN MS as shown in a cohort of 18 patients; lamotrigine at a mean dose of 170mg/day significantly reduced the pain related to TN comparing to carbamazepine. [33] Despite this, a recent systematic review concluded that, there is still no strong evidence to show that the approach to managing TN MS should be different from that for non-MS TN. [18]

Gabapentin belongs to the class of gabapentinoids and acts by blocking some of the voltage-dependent calcium channels. The dose used ranges from 900-3600mg/day.

Gabapentin has been shown to be effective for neuropathic pain, however, strong quality evidence is still lacking for its use in TN. One RCT showed that, combined with ropivicaine, it was effective in a cohort of TN patients. [34] The side effect profile includes cognitive impairment, ataxia, dizziness, somnolence, and weight gain.

Pregabalin is a gabapentinoid that acts as an antagonist of the voltage-dependent calcium channels. In a prospective, open label study, Obermann *et al*, assessed the effects of Pregabalin in patients with TN with (n=14) and without concomitant pain (n=39). Their findings suggest that the antineuropathic effects of pregabalin are similar to those of other antineuropathic agents – of the 53 patients, only 11 had complete pain relief which was maintained after one year. Of interest, patients with concomitant chronic facial pain seem to have had a reduced treatment response which the authors argue could be a predictor for poor treatment response. [35] Pregabalin side effects are similar to those of gabapentin. Its dose ranges from 75-600mg/day.

Gabapentin and pregabalin have been reclassified as class C controlled substances by the UK Government in April 2019, similarly to what some USA states have done in previous years. This decision was based on increased reports of substance misuse and an increased number of deaths linked to its use. [36]

Baclofen is a GABA receptor agonist. It has been studied on an RCT with 10 TN patients and was able to reduce the number of painful episodes when compared to placebo. The small sample size advises caution when interpreting the results. [37] The daily dose usually ranges from 40-80mg, divided in 4 separate doses, and is often used in combination with another anti-epileptic (carbamazepine or oxcarbazepine). [6]

There is weak evidence to support the use of botulinum toxin to reduce the pain intensity in TN. The dose and best method of administration are still not clear. [6]

According to the European Academy of Neurology (EAN) Guidelines, medical management should be trialled before recommending patients for a surgical opinion. It is still not clear how many drugs should be prescribed to patients before a referral to neurosurgery should be made. [5]

Surgical treatment

There are multiple neurosurgical options available for patients with TN (Figure 1.1). The decision to refer patients for a surgical opinion happens if the pharmacological treatment is ineffective, if a therapeutic dose cannot be reached due to side effects or if the medicines are effective but patients cannot tolerate their side effects. It seems, however, that patients undergoing surgery would have preferred to have their surgical procedure earlier on, in their journey. [38] The option of a surgical referral should at least be discussed with the patient early on, even though medical management continues to be the first line of treatment. Patients can make more informed decisions when not in severe pain and not on high dose drugs. In fact, a recent study evaluating the satisfaction of TN patients with a joint consultation clinic with an orofacial pain physician and a neurosurgeon showed that most patients (78%) were overall satisfied with the setting. More specifically, patients found it very helpful to be given an explanation about the surgical options and their complications (76%), and very helpful to be involved (76%) and supported (63%) in the decision-making process. [39]

If a patient requires surgery, the choice is between ablative and non-ablative procedures. It is accepted that the ablative procedures at the level of the Gasserian Ganglion (radiofrequency thermocoagulation, balloon compression and glycerol rhizolysis) will cause a degree of damage to the trigeminal nerve, and therefore cause

changes in the facial sensation. [6] In contrast to MVD, which requires an approximate 4-day hospital stay, these ablative procedures require only a short hospital stay. They are performed under general anaesthetics.

Partial sensory rhizotomy is not frequently performed and internal neurolysis has been suggested as an alternative due to causing fewer side effects. Internal neurolysis requires an approach to the root entry zone via the posterior fossa and when accessed the fascicles of the nerve are separated (longitudinally). This procedure has sometimes been referred to as “nerve combing”. [40]

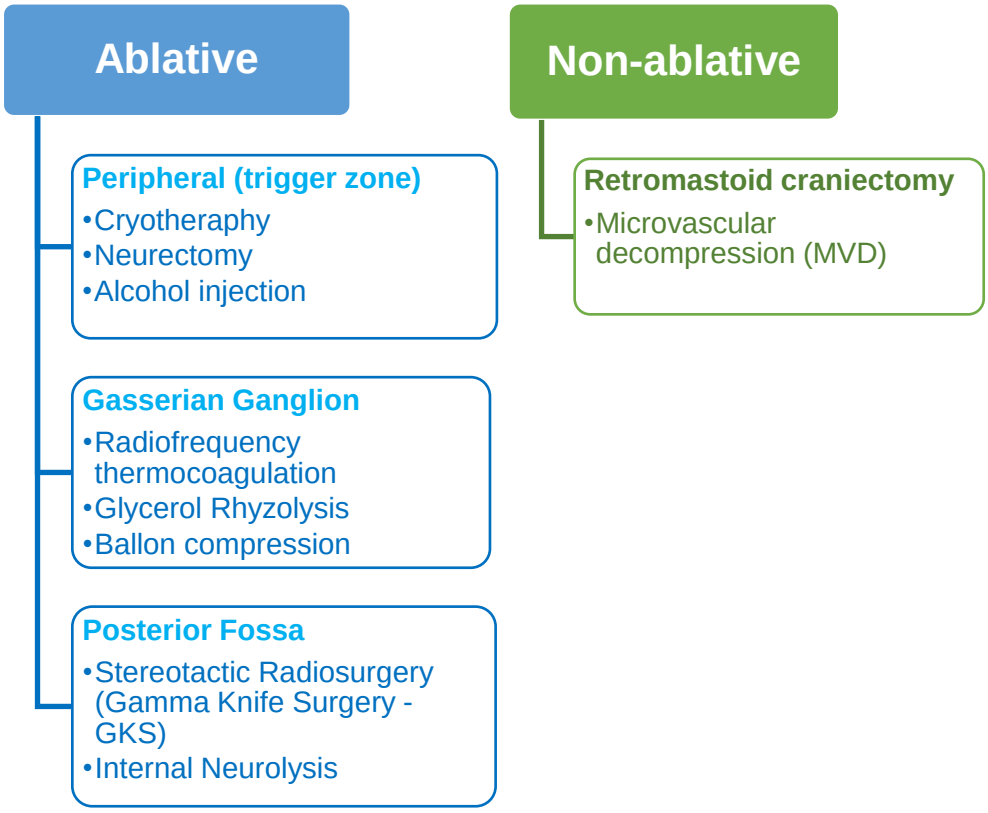

Figure 1.1 Surgical treatments available for the management of TN

The ablative procedures performed at the periphery include cryotherapy, neurectomy and alcohol injection. There is direct lesioning of the terminal branches which can be physical or chemical, and these can also alter the sensation in the face. These procedures are done under local anaesthetic and do not require an overnight stay.

MVD is considered the only non-ablative technique; however, it is a major surgical procedure, where access to the brain stem needs to be gained in order to expose the nerve and proceed with its separation from the impinging vessel. MVD carries a 0.1% mortality risk but more than half of patients might be pain free for up to 10 years. [41] In comparison with the ablative procedures, it is not expected that patients will suffer any sensory loss. The ablative treatments, on the other hand, will cause sensory loss, which in some cases might progress to *anaesthesia dolorosa*. This is more likely to occur following radiofrequency thermocoagulation. [6]

A Cochrane Review in 2011[41] did not find sufficient evidence to make a recommendation on what surgical treatment would offer the best treatment outcome to TN patients but more recently, the European Academy of Neurology recommends MVD over Gamma Knife Surgery (GKS), a non-invasive focused beam of radiation aimed at the trigeminal root entry, in patients with classical and idiopathic TN. Of note, this recommendation is made based on the consistency of results opposed to the quality of the available evidence and it only applies to patients who can and are willing to undergo a surgical procedure. [5]

The efficacy of the different surgical modalities varies and the degree of freedom from pain also varies. Table 1.1, based on data from the European Academy of Neurology guideline on trigeminal neuralgia[5], summarises the outcomes from surgical trials.

Table 1.1 Long term outcomes of surgical trials for TN

Intervention	Number of studies	Total number of patients	Mean follow-up years	Percentage of patients pain free at follow-up	GRADE
MVD	21	5149	3-10.9	62-89	Very low
GKS	8	1168	3.1-5.6	30-66	Very low
RFTC	7	4533	3-9.3	26-82	Very low
BC	5	755	4.2-10.7	55-80	Very low
GC	3	289	4.5-8	19-58	Very low
IN	1	26	3.6	72	Very low

MVD: microvascular decompression; GKS: gamma knife surgery; RFTC: radiofrequency thermocoagulation; BC: balloon compression; GC: glycerol rhizolysis; IN: internal neurolysis

In terms of the side effect/adverse events profile, MVD is the only with an associated risk of death, although very small (0.1%). Additionally, patients can also experience oedema, haematoma, stroke, anaesthesia dolorosa and meningitis. All of these are rare. More common effects are cranial nerve palsy, cerebrospinal fluid leak, hearing loss and facial hypoesthesia. [5] As for the ablative procedures, facial and corneal hypoesthesia, trigeminal motor weakness, meningitis and anaesthesia dolorosa are the most common complications. Of note, the presence of facial hypoesthesia has been associated with better long term prognosis in patients undergoing ablative procedures. [5]

Following surgery, most patients are able to come off their medications but recurrence of pain dictates that medication is re-started and in some instances the same or another surgical procedure needs to be repeated. [42]

1.4 OUTCOME ASSESSMENT

1.4.1 TERMINOLOGY

Outcomes and outcome measures

The Cambridge Dictionary defines an outcome as "the result or effect of an action, situation, or event". In the context of clinical trials, the COMET Initiative (Core Outcome Measures in Effectiveness Trials), describes an outcome as "A measurement or observation used to capture and assess the effect of treatment such as assessment of side effects (risk) or effectiveness (benefits)". [43]

An outcome domain or category is an umbrella term under which more specific dimensions are placed. Throughout the present thesis the term "outcome domain" refers to the overarching classification whereas "outcome" refers to a dimension of that domain: for example, *pain* is an outcome domain, and *pain intensity* an outcome or outcome dimension. Table 1.2 outlines the definitions used throughout the present thesis.

Once the outcome domain and outcome dimension have been identified, the way in which it will be assessed/measured – outcome measure – needs to be defined. According to Zarin *et al*, the full description of an outcome measure should not be restricted to <u>what outcome to use</u> and <u>how to measure it</u>; it should also include information about the <u>metrics</u> (i.e., what change is expected in the patient's results) and the <u>method of aggregation</u>, [44] for example: *Primary outcome: Pain intensity; Outcome measure: on the Brief Pain Inventory, >50% of patients will have a decrease of 3 points on their pain intensity levels, compared to baseline.*

Additionally, a time frame should also be described. Using the above example, *on the Brief Pain Inventory, >50% of patients will have a decrease of 3 points on their pain intensity levels, compared to baseline, at the end of 12 weeks.* [45]

The full specification of an outcome measure is important not only for the accuracy of the proposed study but also to allow replication in similar studies of the same condition. This would contribute to more homogeneous data. [45]

Table 1.2 Outcome definitions used throughout the present thesis

Term	Definition	Example
Outcome domain	This relates to *"What to measure"* This is an umbrella term which accommodates subdomains or outcome dimensions – broad term. A domain can contain many outcome dimensions.	Pain
Outcome dimension	This also relates to *"What to measure"* but is a more specific term. Often referred to as just "outcome".	Pain intensity Pain frequency Pain interference
Outcome measure	This relates to *"How to measure an outcome".* This can be a tool, a questionnaire, or a form.	Numerical rating scale to assess pain intensity

Some entities such as the Food and Drug Administration (FDA) use the term clinical outcome to define outcomes that are used in medical comparative effectiveness research and clinical outcome assessment (COA) to define the assessment of how a patient feels and functions. [46]

Table 1.3 (adapted from the Cochrane Handbook[47] and Patel *et al*[48]*)* outlines the different types of outcomes according to whom the assessor is. In the chronic pain field, given the subjectivity of pain, and the lack of available biomarkers to confirm if a treatment has been effective for chronic pain, the outcomes of the intervention studies will usually be done by asking the patient directly – patient reported outcome (PRO) - by means of questionnaire or form – patient reported outcome measure (PROM).

Table 1.3 Types of outcomes according to the assessor

Outcome type	Definition	Example
Patient reported outcome (PRO)	Reports that come directly from the patient (study subject) without interpretation by anyone else, about their health condition (how they feel or function) or about an intervention or treatment. The information might be obtained through interviews (only information provided by the patient can be recorded), self-completed questionnaires of electronic devices.	Pain intensity
Clinician reported outcome	Reports that come directly from the clinician (health care professional) after evaluating the participant. This involves some judgement or interpretation.	Assessment of an X-ray
Observer reported outcome	Reports that come from an external observer (not the patient nor the clinician/health care professional). It does not involvement judgement or interpretation. The observer might be a family member, a caregiver or an independent researcher.	Result of an automated test

Patient reported outcome measures (PROMs)

A patient reported outcome (PRO) has been defined by the FDA as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else”. [49] A patient reported outcome measure (PROM) is often a questionnaire or a form that the patients complete and which reflect their perspective on the outcome of interest, without the input or interpretation by a clinician or researcher.

The correct utilisation of PROMs has been the subject of much debate. Publications in the field of clinimetrics advocate the correct choice of measurement instruments that should display psychometric properties derived from a rigorous methodological process. [50, 51] Using validated tools to assess a specific treatment outcome in different trials of the same condition, allows for a more homogeneous and transparent combination of results, decreasing variability in study results. The utilisation of general and non-validated tools has been a topic of concern but there is a growing body of research looking at the variation of outcome measures used, their psychometric properties, and their validity to be used in disease-specific trials. Examples of systematic reviews looking at the psychometric performance of PROMS can be found in lower back pain[52], headaches[53], neuropathic pain[54], musculoskeletal related pain[55] and complex regional pain syndrome (CRPS) [56] fields. There is also a growing body of literature on the translation and cross-cultural adaptation of questionnaires, which suggests that there is a global understanding of the importance of valid and reliable questionnaires for outcome assessment. Examples span from Africa[57] and Europe[58] to South America[59] and Asia. [60]

Regulatory agencies such as the FDA support the use of patient reported outcome measures for approval of medical products. [46] Nevertheless, the COAs need to go through a thorough development/validation process as illustrated by the “Roadmap to Patient-Focused Outcome Measurement in Clinical Trials”, developed by the agency’s Clinical Outcome Assessment team. This “Roadmap” outlines a stepwise approach to the development of patient outcome measurement in clinical trials. There are key stages where patients or their carers have a fundamental role to play: providing insight of the impact of disease, sharing their definition of treatment success, helping to identify what the concept (s) of interest are (for example, how a patient feels or

functions). [61]The COSMIN initiative (COnsensus-based Standards for the selection of health Measurement Instruments) is dedicated to developing tools based on meticulous methodology to guide authors in validating and selecting the correct tool to measure the outcome of interest. [62] Through an international study, the COSMIN initiative has reached consensus on the taxonomy, terminology, and definition of the measurement properties of patient reported outcomes. According to this study there are three main domains which should be assessed (validity, reliability, and responsiveness). Table 1.4 includes the agreed definitions. [63]

Table 1.4 Domains, measurement properties, and aspects of measurement properties

Term			Definition
Domain	**Measurement property**	**Aspect of a measurement property**	
RELIABILITY			The degree to which the measurement is free from measurement error
Reliability (extended definition)			The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: for example, using different sets of items from the same HR-PROs (internal consistency), over time (test–retest) by different persons on the same occasion (interrater) or by the same persons (i.e., raters or responders) on different occasions (intrarater)
	Internal consistency		The degree of the interrelatedness among the items
	Reliability		The proportion of the total variance in the measurements which is because of “true” differences among patients
	Measurement error		The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured
VALIDITY			The degree to which a PRO instrument measures the construct(s) it purports to measure
	Content validity		The degree to which the content of a PRO instrument is an adequate reflection of the construct to be measured
		Face validity	The degree to which (the items of) a PRO instrument indeed looks as though they are an adequate reflection of the construct to be measured
	Construct validity		The degree to which the scores of a PRO instrument are consistent with hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the PRO instrument validly measures the construct to be measured
		Structural validity	The degree to which the scores of a PRO instrument are an adequate reflection of the dimensionality of the construct to be measured
		Hypotheses testing	Idem construct validity
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted PRO instrument are an adequate reflection of the performance of the items of the original version of the PRO instrument
	Criterion validity		The degree to which the scores of a PRO instrument are an adequate reflection of a “gold standard”
RESPONSIVENESS			The ability of a PRO instrument to detect change over time in the construct to be measured
	Responsiveness		Idem responsiveness
Interpretability*			*The degree to which one can assign qualitative meaning—that is, clinical or commonly understood connotations—to an instrument's quantitative scores or change in scores.*
*Not a measurement property but an important instrument characteristic			

For chronic pain, most of the outcomes will be subjective and their assessment, via patient questionnaires/scales, should be as reliable and as valid as any objective outcome measure. [61] As seen in Table 1.4, there are different types of validity, but these are not all equally relevant for assessing pain and their related constructs. For example, criterion validity would not traditionally be assessed as there is no criterion or "gold standard" with which pain ratings can be compared, therefore this is usually not relevant. [64] In contrast, and according to COSMIN and to the FDA, content validity is the most important measurement property to assess. [65] Content validity refers to the extent to which a questionnaire is relevant, comprehensible and comprehensive. Dworkin and colleagues, argue, however, that although a pain intensity scale might demonstrate content validity, for example, this might be true only in certain populations. The explanation lies in the fact that the experience of pain might differ among different populations where the construct of pain might have different meanings i.e., unidimensional vs multidimensional construct. In addition to this, there is usually a lack of guidance on how the PROMs should be completed as there is usually no time or resources to educate participants in how to best complete them. [64] The final aspect of validity is construct validity. This, as stated in Table 1.4, refers to the extent to which the score of the questionnaire is consistent with previous hypothesis. For example, how scores of a PROM relate to scores of questionnaires assessing related constructs or how the scores might be similar or dissimilar in different populations. According to Dworkin and colleagues, when attempting to improve the content validity of a pain intensity scale, for example, one should remember that the pain experience will be impacted by different factors such as duration and interference of pain, individual characteristics such as coping, and the patient's social circumstances. [64]

When adapting a PROM to be used in a different language or in a different culture, the scores should reflect the performance of the original one. However, it is important to acknowledge the cultural differences in pain beliefs that exists in different countries or cultures. [66]

Finally, in addition to above mentioned aspects of construct validity, a note should be made about convergent and discriminant validities. According to Paul Krabbe, convergent validity refers to how closely a questionnaire/scale relates to other variables of the same construct and discriminant validity refers to how scores of questionnaires assessing different constructs should not be related. [67] More specifically, constructs that theoretically should not be related are, in fact, unrelated. [68] For example, there might be constructs which are related to pain intensity levels (convergent validity) or those which are not (discriminant). Pain related constructs include for example pain interference, and unrelated constructs include physical and emotional functioning or even sleep quality. [64] In addition to validity, the questionnaires should demonstrate reliability (the scores of the instrument do not change when patients are stable, despite possible changes in the timing of the measurement and the instrument rater) and responsiveness (if there is a change in the construct of interest, for example due to a new treatment, the instrument is able to detect it). The questionnaires should also be easy to interpret and be feasible to use without causing excessive burden on patients or clinicians. [69] Interpretability and feasibility are not measurement properties but important characteristics of the instruments/questionnaires. If there is a change in scores of a questionnaire, the interpretability of this change can be enhanced with the reporting of the minimal important change/ minimum clinically important difference.

An explanation on the criteria for good measurement properties of PROMS is expanded on in Chapter 4.

Primary and secondary outcomes

When designing a study, it is crucial that the outcomes of interest are defined *a priori*, at the time of trial design and protocol preparation. [70] The primary outcome, as defined by ClinicalTrials.gov, is the most important to evaluate the effectiveness and/or safety of the intervention or treatment. [71] It should be the one that answers the research question and it should be relevant to patients and/or clinicians. [43] The primary outcome is also the one used for power calculation. Usually there is only one primary outcome in a clinical study, however, some studies may have more than one. There are some considerations when choosing more than one primary outcome, as it can give rise to an unfocused research question and in turn to an unfocused study, and it can also cause problems of interpretability as multiple analyses are needed. [45]

Apart from the primary outcome, other outcomes might be assessed, and they are known as secondary outcomes. These outcomes may demonstrate additional effects of the treatment or intervention on someone's health status, [72] for example adverse events.

1.4.2 OUTCOME ASSESSMENT IN CLINICAL TRIALS

Clinical research or clinical studies are designed with the aim of contributing to increased medical knowledge. The research might provide information to improve diagnostic skills, understand how to prevent diseases or identify the best treatment for a certain condition. In clinical studies where a treatment is being tested, classified as an interventional study, the ones with the potential to reach results with the strongest level of evidence and which remains the gold standard, are randomized controlled trials (RCTs). [73] In these types of trials, two or more groups are randomly assigned to receive either a treatment or intervention under investigation or another treatment or a placebo or even no treatment at all. The effects of treatment – outcomes of treatment – are assessed statistically and comparisons between groups are made. It is hoped that differences between groups will be found, and that these are not only statistically significant, but also clinically relevant. Importantly, the outcomes of treatment should be meaningful to patients. It is therefore clear that the choice of outcomes, and how the assessment of these outcomes is made, is extremely important. The validity of the results and the validity of the trial depend on rigorous planning and transparency in reporting, to minimise bias. There are many factors which can contribute to biased results in RCTs:

- Randomisation process,
- Deviation from the intended interventions,
- Missing outcome data,
- Measurement of outcomes – choice and timing,
- Loss of blinding,
- Selection of the results to report.

Rigorous planning and transparency in reporting is therefore essential. A systematic review of studies comparing outcomes defined in a trial registry with the finalised published trial outcomes highlighted the discrepancies in the outcome utilisation. For example, four of the reviewed studies observed changes in the registered and published outcomes in more than 50% of the analysed studies. [74] While there are justifiable reasons for a change of outcomes during a trial, modifying the protocol without clearly acknowledging it raises the question of outcome reporting and publication bias. Furthermore, the outcomes used do not always reflect what the patient considers important nor are they relevant to make a critical decision about clinical care. These factors add to the poor utilisation of resources and waste of research results. [43]

Well-designed RCTs of a given condition collecting the same outcome domains, generate more homogeneous data which can be combined in meta-analyses. Indeed, this statistical procedure, which allows data from different studies to be integrated, is at the top of the hierarchy of evidence. Even if the results of the individual trials are not apparent, their integration via meta-analysis generates an overall estimate of the benefit/harm of an intervention, which is more precise than the results of the individual studies. [75]

To minimize the discrepancy between studies and results, groups of researchers and clinicians have developed guidelines for the systematic reporting of outcome measures. One such example is the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), which has developed recommendations for core outcome domains to be reported in clinical trials of pain disorders. [76]

Although the guidance from IMMPACT is a good starting point, it continues to be necessary to work with individual patient cohorts to understand more about the impact of their disease and what aspects of their pain matter the most, i.e., which specific dimensions should be under the "pain" domain. As stated by the authors, "*There are several dimensions of pain that can be assessed in a clinical trial (e.g., intensity, location, specific descriptors and qualities)".* Not all dimensions of pain need to be investigated in all chronic pain trials. If someone suffers with persistent lower back pain, frequency of pain episodes will matter less in contrast with someone who suffers with trigeminal neuralgia.

1.4.3 CHALLENGES TO CONSIDER IN TRIGEMINAL NEURALGIA RESEARCH

Disease characteristics – general and specific

Trigeminal neuralgia is a rare disease and as such, one of the common challenges when trying to set up a clinical trial is related to the limited access to resources including access to funding. [77] Another challenge is related to the recruitment and retention of patients to take part in clinical trials. First, as a rare disease, the pool of potential participants is not large. [78] Secondly, patients with high intensity paroxysms and those in remission who might relapse are likely reluctant to participate, and to try either the drugs being developed or placebo, fearing that they might experience exacerbated levels of pain. [77, 79] Trials with a small sample size would be easier to set up, less expensive and more likely to be concluded, however, the data would have diminished statistical power and clinically significant effects would possibly not be detected, giving rise to results which are less reliable, and which are more difficult to generalise. [79, 80]

The multiple TN classifications, suggested over the years, have posed yet another challenge. Inclusion and exclusion criteria, based on the most up to date classification or, based on no specific classification, gives rise to heterogeneity of the data gathered. [78] Additionally, the number of researchers or clinical researchers with an interest and expertise in TN is small which can therefore lead to inaccuracies in the identification and correct diagnosis of patients with TN.

Finally, the surgical and pharmacological treatments currently available are difficult to compare. The side effect profile of medicines and surgeries is quite different and has a different impact on patient's lives, a 50% reduction of pain from medication therapy is acceptable but for surgery 100% pain relief is expected.

Primary outcome

In chronic pain clinical trials, pain intensity is the most likely primary outcome. [48] In the TN field, researchers have used pain intensity and pain relief as the primary outcome, however, there seems to be no consensus as to what the primary outcome dimension in TN trials should be. Studies that use either pain intensity or pain relief as their outcome of interest are difficult to compare. Pain intensity refers to "how intense the pain is" or, as defined by Jensen and Karoly, "how much a person hurts", [48] whereas pain relief refers to "how much pain relief" has resulted from a certain treatment. [81] Some authors have attempted to clarify if pain relief ratings and pain intensity ratings are comparable. For example, Jensen *et al*, looked at a cohort of 248 post-surgical patients (knee replacement vs laparoscopy) whose outcomes were pain intensity (Visual Analogue Scale – VAS, and Verbal Rating Scale - VRS) and pain relief (VAS).

They had hypothesised that the differences in sensitivity to detect change would be similar in both cohorts, however, this was not supported. They have confirmed that even though related, pain relief and intensity mean slightly different things, as patients report pain relief even when pain intensity ratings are the same or even higher than pre-surgery. Their conclusions point to the need of a clear definition of the primary outcome and a clear choice of a validated tool capable of capturing it. [82] Additionally, pain intensity may remain the same but the patient's ability to cope with it may change and this would be reflected in measures assessing aspects such as health related quality of life (HRQOL).

It may be that TN trials could include two primary outcomes – pain intensity and pain relief – and it would be interesting to see if these would correlate in this cohort of patients. However, as TN is a unique type of neuropathic pain, in which patients can have episodic pain attacks, with some going into remission periods, in addition to pain intensity and pain relief, pain frequency might also be an outcome of high importance. This has been highlighted in a recent double-blind, multicentre, placebo-controlled, randomised withdrawal phase 2a trial of vixotrigene. [25]

Outcome assessment

There are very few randomised controlled trials, comparing the different drugs[83], drugs and surgery or the different surgical procedures, and this partly explains the lack of a clear choice when it comes to treatment. Additionally, the lack of standardised outcomes and outcome measures used contributes to the heterogeneity of data and the growing inability to compare study results. A recent randomised controlled trial assessing the hypothetical superiority of balloon compression over radiofrequency in

the treatment of TN could not demonstrate that, for the primary outcome (worst pain level over the last 24 hours, at the 180-day evaluation, measured on an 11-point numerical rating scale of the Brief Pain Inventory), there were statistically significant differences between both procedures. [84] As for the secondary outcomes, there were also no statistically significant differences between both groups. The explanation for these results is likely twofold: the small sample size and the choice of outcome measures for primary and secondary endpoints. Although a numerical rating scale is appropriate for pain intensity as recommended by IMMPACT, the secondary outcomes, and secondary outcome measures were chosen without prior validation by patients. As an example, some of the items on the pain interference scale on BPI are not relevant for TN patients, for example the impact of pain on their walking ability. [85] Details like this can interfere in the psychometric performance of a questionnaire and render it not valid to use in this cohort of patients.

The need for more standardised outcomes and for the assessment of end points other than those related to alleviation of pain has been highlighted over the years in the TN literature[21], e.g. neurology guidelines, [4, 5] and more broadly, in the chronic pain field[86] yet, there is still no consensus regarding what outcomes should be measured and how to measure them. The lack of information on outcomes fails to provide patients with adequate answers about the prognosis of the treatment options available and adds to research waste. These research challenges could be improved if the wider research community assessed the same outcomes in a standardised way.

1.5 CORE OUTCOME SETS

The transparent reporting of clinical trials has improved over the years and the CONSORT (CONSOLIdated Standards of Reporting Trials) statement, for example, provides evidence and guidance on how best to report RCTs in order to minimise bias. [87] To increase consistency and transparency in research, the website ClinicalTrials.gov was created in the year 2000, a platform where prospective studies should be registered. [74] Despite these attempts, outcome reporting is still far from ideal. According to Tugwell and Boers, "*Clinical trials are only as credible as their outcomes",* so to improve the reporting of research studies, several authors advocate the use of a Core Outcome Set. A Core Outcome Set (COS) is defined by the COMET Initiative as "*an agreed and standardised set of outcomes that should be used, as a minimum, in all trials of a specific condition*." [43]

The advantages of a COS are[88]:

- Less heterogeneity of studies, which improves meta-analysis;
- Lower risk of reporting bias;
- More clinically relevant outcomes are identified as relevant stakeholders are involved in the decision-making process.

The COMET initiative was launched in 2010 and its aim was to raise awareness to the issues caused by heterogeneity in outcome reporting while encouraging the development and uptake of COS by offering methodological guidance to do so. The COMET methodology has applications in different health/research areas. Similar initiatives originated from the lack of guidance in specific health areas to improve outcome measurement utilisation; this is the case of the OMERACT group (Outcome Measures in Rheumatology), IMMPACT and the CROWN initiative (Core Outcomes

in Women's Health). One of the advantages of a COS is that it involves different stakeholders, more specifically patients, and this can make a huge difference on the selected outcomes. For example, guidelines for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults, by the International Headache Society, suggest that the primary outcome should be a change from baseline in the number of migraine days. Migraine severity or migraine intensity are classed as secondary outcomes, and although functional impact and impairment are included as secondary outcomes, there is no mention of quality of life assessment. [89] In contrast, the recently developed core outcome set includes pain and migraine specific quality of life as its two core domains. Pain intensity and number of migraine days are the specific pain dimensions. [90] This example illustrates the importance of involving different stakeholders in the choice of outcomes, and specifically patients, as the results might differ, if not significantly, at least slightly but enough to be of greater meaning to the patients.

According to the guidance provided by the COMET initiative, the first step in developing a COS is to identify the scope of the COS i.e. the target population, the type of intervention and the setting of the intervention. Arguably, the process of identifying the outcomes that should be reported as a minimum might follow rigorous planning but there are other factors which can impact on the quality of the data generated in a clinical trial. Some of these have been discussed in previous sections of the present thesis, such as different disease classification systems and diagnostic criteria, which can dictate inclusion and exclusion criteria of clinical trials. Although these factors need to be acknowledged here, and certainly, the use of COS is not the only way of improving research results, the use of COS is without a doubt an important step.

1.6 SUMMARY

The correct outcome assessment in clinical trials can be challenging. Some of these challenges are generic and some condition specific. There is, however, a growing body of evidence to mitigate these and a core outcome set is certainly one of the solutions, especially for a rare disease, such as trigeminal neuralgia. In Chapter 2, the methodology used to develop the core outcome set for trigeminal neuralgia is described.

CHAPTER 2 METHODOLOGY – AN OVERVIEW

2.1 OVERVIEW

To develop a core outcome set it is important to involve key stakeholders who can prioritise outcomes which later are going to go through a consensus process which will reduce large numbers of outcomes to a small set of the ones deemed crucial to be used in future studies of a specific disease. Although guidance exists on how to develop a Core Outcome Set (COS), the best approach or gold standard is yet to be identified. A variety of methodologies have been used by COS developers. [43] A systematic review of 198 studies on the choice of important health outcomes in effectiveness research identified a wide range of methods within publications up to 2013. [91] Mixed methods were used in 74/198 studies. Others used semi-structured (n=57) or unstructured (n=18) group discussions only; consensus conferences only (n=12), literature/systematic reviews only (n=11) or Delphi survey only (n=6). In the mixed methods group, there were different methods used in combination, for example, a Delphi survey and literature/systematic review; a consensus conference and a survey; focus group work and a rating exercise. It is still not clear yet, however, if different methodologies would create similar results, or if there is any advantage of using one methodology over another. [43]

This Chapter provides an overview of the theoretical and methodological frameworks that were the blueprint for the development of the TN core outcome set, the study's overall aim. It then expands on the specific methods to achieve that aim.

2.2 THEORETICAL AND METHODOLOGICAL FRAMEWORKS

2.2.1 Biopsychosocial model of chronic pain

The biopsychosocial model of pain was originally described by John Loeser and Gordon Waddell. These two surgeons observed that surgery for lower back pain was unsuccessful, and the pain experienced by the patients could not be explained by pathology alone. They considered that other contributors were likely to be playing a role in the patients' symptoms, for example, "the stress of his or her environment". [92] Since then, and in the past 40 years, the biopsychosocial model of chronic pain has been widely used to aid the understanding of the aetiology, prognosis, assessment and management of chronic pain. [93] This is the most widely accepted model to explain the interplay between biological, psychological and social constructs which play a role in chronic pain illness and moves away from the long-established biomedical model which stipulated a direct relationship between tissue injury and pain. [93]

The wider pain community has been focused on exploring outcomes of treatment other than pain intensity (e.g. quality of life, social interactions, sleep, fatigue) and multiple collaborations with patients are underway to fully understand the extent of the disability caused by their chronic pain condition, for example, in the fields of migraine, [94, 95] non-specific lower back pain, [96] and complex regional pain syndrome. [97] The field of orofacial pain is no exception, and there is evidence that anxiety and depression are comorbidities present in those diagnosed with burning mouth syndrome and temporomandibular disorders. [98-100]

The biopsychosocial model is the main theoretical framework underpinning the development of the TN COS.

The ‘biological’ domain refers to nociceptive, neuropathic and nociplastic mechanisms, as well as to genetics, age, and neurochemistry. The ‘psychological’ domain includes constructs such as anxiety, depression, catastrophising and self-efficacy. The ‘social’ domain includes for example social/family support, social withdrawal, employment factors, and exclusion stigma/discrimination. Examples of the relationship between the above-mentioned domains and constructs are given below.

Psychological constructs

The biopsychosocial model has not been specifically validated in TN, but there is evidence of the impact of TN on mental well-being, and it was anticipated that stakeholders involved in the present work would prioritise outcomes other than pain intensity/relief. One TN study reported outcome data of 225 patients and identified that more than 50% had anxiety, and a high proportion of patients showed negative thoughts about their pain, on the Pain Catastrophising Scale (PCS) (146/188). [101] In this specific example, it is not possible to make an association between catastrophising and its mediating effects in other pain related constructs but there are many examples in the literature which provide evidence for this. In relation to pain, catastrophising has been defined by Sullivan as *“an exaggerated negative mental set brought to bear during actual or anticipated painful experience”.* [102] Catastrophising can influence pain related outcomes and it has been shown to be a risk factor for the development of chronic pain. It has also been associated with worse post-surgical outcomes when present pre-treatment in breast cancer and knee arthroplasty cohorts.

It has also been associated with higher pain intensity and it correlates negatively with more “positive” constructs such as self-efficacy. [103] For example, high catastrophising levels and low self-efficacy levels have been identified in temporomandibular disorder cohorts. [104] Self-efficacy can be defined as “*an individual’s belief in his or her own ability to perform a certain behaviour to achieve a desired outcome”* and has been identified as a positive and protective construct. [103] Examples of the role of self-efficacy as a mediator between pain intensity and disability exist in the headache and fibromyalgia fields. [103] There is also evidence of the role of self-efficacy in the orofacial pain field. An RCT investigated mediators, moderators, and predictors of treatment effects of cognitive behavioural therapy (CBT) for chronic temporomandibular disorder pain. The outcomes under assessment were pain intensity, activity interference and jaw movement. Mediators under investigation were self-efficacy, pain beliefs, pain catastrophising and coping. Self-efficacy was the mediator more strongly associated with improved levels of pain and therefore decreased levels of disability when compared with the other variables, in the CBT group. [105] A recent study of a six-session CBT group programme for TN patients highlighted its potential benefit in reducing the negative beliefs about pain and participants felt more confident in self-managing their symptoms. [106] Although this was a preliminary feasibility study done with 15 patients, the high levels of patient satisfaction at the end should encourage further studies on psychological interventions in the management of TN.

Another study looking at the burden of illness of TN identified that patients who completed the PENN-Facial Pain Scale – Revised (Penn-FPS-R) (77/127) indicating pain interference had worse quality of life as reported on the EuroQol 5 Dimensions 5 Levels index (EQ-5D-5L), when compared to those reporting no pain interference (0.80, SD = 0.21 versus 0.96, SD = 0.14, respectively). [42]

Biological constructs

The biological treatments within the context of the biopsychosocial model as a framework for the management of chronic pain have often included surgery, nerve blocks, and/or pharmacotherapy. [92] These treatments are aimed at reducing pain levels. There are other biological constructs, such as age, genetics, central nervous system biochemistry and pain mechanisms which might influence the experience of pain and the outcomes of treatment might be varied due to biological variance.

With some exceptions recently published in the literature, describing the multidisciplinary management of TN[107, 108], its treatment still largely follows the biomedical model and most studies describing the implementation and/or effectiveness of pharmacological and/or surgical treatments assess the effects of these treatments on pain intensity levels or on the degree of pain relief.

As described in Chapter 1, the exact mechanism for the development of TN has not been identified yet. There is evidence of the role of sodium channels, due to the effects of sodium channel blockers on pain levels and pain relief outcomes. These drugs, however, seem to have little effect on concomitant continuous pain that some of the TN patients experience, and this has been linked to mechanisms of central sensitization. [14]

TN is also more prevalent in middle age to older adults, and there are age related considerations to be had when treatments are chosen in this cohort of patients. In this age group, the prevalence of other chronic diseases is higher, and patients are likely those needing polypharmacy. In addition to this, TN is more prevalent in females. Increased age, female sex and a high number of medical comorbidities are associated with increased rates of chronic pain. [109]

Social constructs

As stated above, outcomes relating to social health are far less reported than those constructs under the biological and psychological domains. The interpersonal context is said to modulate the experience of pain but little is known about how this occurs. [110]

A qualitative study of 16 patients with TN identified “isolation and social withdrawal” as one of the four interpreted themes. Patients in this study felt that they had to withdraw from social activities as either a consequence of their pain or in fear that their pain might develop when in social gatherings. Although many participants felt supported by their relatives, high pain intensity levels created difficulties in social interactions and caused isolation. [111] A retrospective study of clinical records from 675 pain patients (with 15.9% being orofacial pain patients) looked at the mediator role of physical function and satisfaction with social roles and activities between pain intensity and depression and anger. The results indicated that higher scores of social satisfaction predicted lower levels of depression and anger. Additionally, satisfaction with social roles mediated the relationship between pain and anger and pain and depression at a statistically significant level. [112]

Chronic pain patients very often report frustration with suffering with an “invisible” condition. [113] The “invisibility” of chronic pain might generate misunderstandings, disbelief and give rise to workplace conflicts and stigma. [114] Stigma can be experienced not only in workplace settings but also in social circumstances and inclusively in medical settings. Stigma can exacerbate social isolation and withdrawal. In the chronic pain clinical context, stigma can give rise to poor pain management on the account of disbelief of complaints on pain intensity levels or extent of disability. [115]

The social consequences of pain can impact directly on outcomes of treatment, as they may impact on patient's ability to seek treatment, to comply with treatment and to engage in self-management. [114]

As seen above there are complex and intricate relationships between the three domains on the biopsychosocial model. An attempt has been made over the years to use the model as the underpinning framework to guide multimodal treatment for chronic pain, but biological and psychological constructs seem to be targeted more often than social constructs. [92] A systematic review of outcomes reported in multimodal pain therapy for chronic pain, reports that outcomes related to the social health core area (e.g., satisfaction with social roles and activities) were reported in fewer than 10% of the studies assessed (n=70). [116]

To aid researchers in assessing the benefits and harms of chronic pain treatments, given the complexity of pain assessment, the IMMPACT initiative, through a consensus process with experts with diverse knowledge in chronic pain, identified 6 core domains which should be reported in chronic pain clinical trials. These are: pain, emotional functioning, physical functioning, symptoms and adverse events, participant ratings of global improvement and satisfaction with treatment and finally, although not specifically an outcome, participant disposition (navigation of participants through a trial). [86] Supplemental domains have been suggested by IMMPACT, for example, coping, role and interpersonal functioning. Although these core outcome domains are a helpful starting point, these are not condition specific and their suggestion as a core group has had little input from patients, therefore they do not necessarily map to the different constructs in the biopsychosocial model of pain.

Although the IMMPACT core outcome domains were used to map findings of the initial stages of the present work, the data collection was not restricted by it and development of the core outcome set was mostly approached with the biopsychosocial model as a theoretical framework.

In summary, the biopsychosocial model of pain underpins the development of the TN core outcome set, given the complexity in assessing and treating patients with chronic pain, who likely need a comprehensive approach to assess different life domains where pain and it's treatments can have an impact and without which researchers are unlikely to obtain meaningful results of treatment. [117]

2.2.2 Methodological framework

As described in this Chapter's introduction, there is no gold standard methodology to develop a COS, however, guidance has been provided mainly by two groups – the COMET Initiative and OMERACT. [43] Based on these two initiatives' guidance, COS have been developed for clinical trials of paediatric chronic pain[118], hip/knee osteoarthritis[119], gastric[120] and anal cancer[121], just to name a few. Work is underway to develop COS for temporomandibular disorder (TMD) [122] and burning mouth syndrome (BMS) [123], based on the aforementioned guidance.

OMERACT was established in 1992 to improve outcome measurement in rheumatoid arthritis, as comparisons between endpoints in European and North American clinical trials differed hugely. It has since expanded to include other rheumatological diseases. [124] The group published a handbook (OMERACT Handbook, current version 2.1 April 2021) where methodological guidance is outlined. [124]

The COMET initiative had its inception in 2010 and it aimed to improve the awareness of outcome related problems in research, promote the involvement of patients and the public in research, encourage COS development by providing resources to help researchers develop COS, decrease repetition of COS development for the same disease by creating a database for registration of studies and provide guidance for COS development based on up to date evidence. [43] In addition to the database, the COMET group has also made some resources available to aid those involved in COS development to follow a structured process, for example, the COMET Handbook (version 1.0) [43], the COS-STAR (Core Outcome Set–STAndards for Reporting: The COS-STAR Statement). Chapter 6 follows the COS-STAR standards for reporting of the present study's results. [125]

Study overview

Chronic pain disorders share many similarities, but it would be a mistake not to acknowledge the specific/individual disease characteristics in trigeminal neuralgia. As such, guidance was sought from COMET and used as the study's methodological framework. COMET endorses identification of the most important outcome domains for the specific patient population, and other important stakeholders.

Stakeholders involved in a COS development process should be: (1) those who are going to be using the COS in future studies, for example, trialists and researchers, (2) health care professionals who are the ones involved in the shared decision making when it comes to treatment decisions in real world settings and (3) health service users as in patients or their representatives.

To reach a final list of outcomes which are to be part of the core outcome set it was necessary to start by reviewing what had been published to date. Specifically, information on what outcomes had been used to date, had to be retrieved – secondary data analysis. This was done by completing a systematic review of intervention studies to summarise the outcomes and outcome measures (Chapter 3). ClinicalTrials.gov website was also consulted to confirm if any recently published trial protocols displayed outcomes not identified through the systematic review. After identifying the outcomes and the questionnaires used, a new systematic review was done to investigate the psychometric properties of the questionnaires used in the TN field (Chapter 4).

Following the collection of the background information, primary data were collected: a qualitative study with patients was conducted to confirm if the outcomes used to date mapped those considered important to patients (Chapter 5) and, finally, quantitative data were generated, by asking different stakeholders (patients, clinicians and researchers) to score the importance of outcomes during an online Delphi survey and by making a final decision as to what outcomes should be part of the COS during an online consensus meeting (Chapter 6). Figure 2.1 illustrates the study overview based on the COS development process outlined in the COMET Handbook. [43]

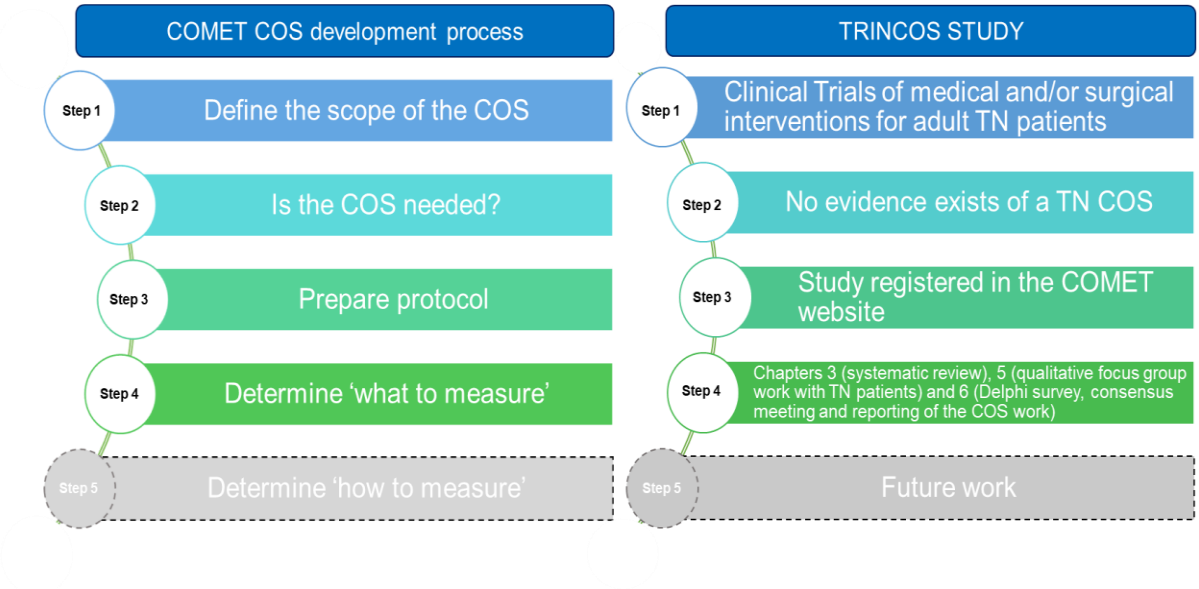

Figure 2.1 Flow chart of the study stages mapped to COMET COS development process

2.3 MIXED METHODS

The combination of the above primary data collection methods (qualitative and quantitative) is under the umbrella of mixed methods approach to research.

Mixed methods research had its formal inception around the late 1980s, in education, sociology and management disciplines, although, the methodology had been used with a different nomenclature during the first 60 years of the 20th century, especially in sociology and anthropology. [126]

Mixed methods research refers to the combination of quantitative and qualitative research methods, through collection, analysis, and interpretation of qualitative and quantitative data [127, 128] and it is considered a distinct third research approach. It developed as a way of providing validity to qualitative studies and researchers were keen to develop new methodologies which incorporated the qualitative and quantitative perspectives, when one of the methodological approaches could not explain or make sense of the data collected using the other approach. [128]

The use of quantitative or qualitative data collection methods alone would not permit reaching this study's aims. The combination of both types of data not only contributed to achieve the proposed aims but it also strengthened our results. On one hand, it was important to collect detailed and in-depth knowledge, specifically, patients' preferences of outcomes of treatment as well as the description of their lived experience, something achieved only by qualitative methods for data collection and analysis. [129] Numerical data were subsequently collected; this was achieved during the online Delphi survey and online consensus meeting. Quantitative methods can give rise to data which can be generalizable, and one can draw conclusions on the

magnitude of the results. Quantitative methods can also validate data collected with qualitative methods.

2.3.1 MIXED METHODS DESIGN

An exploratory sequential mixed methods design was used. There are two phases of data collection: first, qualitative data are collected, analysed and interpreted and used to inform the second phase, where quantitative data are collected. [128] In this study's specific example, qualitative data were collected with focus group work with TN patients. Data on the patient's lived experiences and their preferences of outcomes were used to design the Delphi survey. Integration of data was done through building, which happens when the results of one type of data informs or builds on the data collection of the other type of data. [129]

QUALITATIVE DATA COLLECTION – Overview

Focus Groups

Focus groups are a method for qualitative data collection, and as such, share strengths with other qualitative data collection methods: ability to explore a topic in depth, discover new knowledge about a group of people, exploration of the participants context which influences their answers within the group discussion and interpretation of the different points of views among participants. [130]

Focus group work consists of an informal discussion about a given topic. There is usually a moderator who guides the discussion by using open end questions, based on a topic guide.

It is recommended that focus group discussions involve 6-8 participants. Although each person shares their view on the given topic, the advantage of focus group methods is that the data generated also originate from the interaction between participants in response to one another, and between the participants and the moderator. This is a distinctive approach compared to one-to-one interviews.

Although focus group work was popular in the social sciences and education and in marketing research, specially, before the late 70s, it has now become popular in the health sciences and in evaluation of health services. [131] For example, focus group work has been used to understand participants' experiences of disease, what their knowledge is about a given illness or even their perception of health services. [132] A full description of the focus group work with patients, including its limitations, is presented in Chapter 5.

QUANTITATIVE DATA COLLECTION – Overview

Consensus Methods

Consensus methods are an approach to gather consensus on a given matter by a group of individuals who are considered experts. Their expertise can be professional or personal. Examples of formal consensus methods are the Delphi technique, nominal group technique and consensus conferences. [133] The Delphi technique and a consensus meeting were the methods of choice for the present study.

In the evidence based medicine hierarchy pyramid, expert opinion is placed at the bottom, with a Level 5 classification, however, consensus methods are important when there is either a lack of scientific knowledge to explain a phenomenon or the knowledge that exists is contradictory. [134] Higher levels of evidence can be achieved with research that builds on knowledge achieved with consensus processes, either to validate it or to refute it. [135]

Delphi Method

The Delphi method had its origins in the 1950s and it was developed by the RAND corporation. It was used to understand how technology could impact warfare, but it has been used in many different fields since, for example, education, health care and management. [135] It consists of a series of questionnaires presented to a group of experts, who answer them anonymously. It can have several rounds, but it needs at least two. [43] After each round the results are incorporated on the subsequent round, and the participants have the opportunity to reflect on their voting in light of the other participants' responses. [136]

In the context of a COS development study, the Delphi method is used to obtain the opinion of the participants on the importance of the outcomes presented, with the aim of achieving consensus, or at least, to prioritise some of the outcomes from the original list. Currently, the questionnaires can be circulated electronically and there are software packages available to facilitate the distribution, data collection and data analysis. [137] The advantage of using an electronic version is that it can reach a geographically diverse group of experts. [136] The definition of consensus should be defined a priori, and different definitions are available in the literature. By the end of the process, descriptive statistics are used to identify which outcomes have reached consensus, to be included in the COS.

Consensus meetings/conferences

A consensus meeting is a process by which a group of people, usually experts on a given subject, meet face to face (or online) to debate, discuss and generate agreement on a given issue. By the end of the meeting, the group should reach a consensus, which differs from unanimity. That is, not all participants are unanimous in terms of the preferences, but there is a shared agreement by all.

A consensus meeting can take place following a Delphi survey, if the COS development team decides to do so. In this context, the consensus meetings, which can be held face to face or online, allows participants to discuss the results of the Delphi survey and to finalise the list of outcomes to be part of the COS. There is no specific guidance on how to run these meetings, some follow a formal structure, such as nominal group technique, and some are more informal discussions, followed by voting. In view of the recent need to shift to online meetings, some COS developers

have organised either hybrid or pure online consensus meetings, and COMET prepared a document on issues to consider with online meetings, following input from many COS research team members. [138]

2.4 DISCUSSION

Using mixed qualitative and quantitative research methods can be challenging due to time and resources needed. It is important to have a multidisciplinary team familiar with the different types of research methods. When gaps in knowledge are identified, training should be sought to improve the ability of the team members to conduct data collection, data analysis and data synthesis or integration. In the present study an exploratory sequential mixed methods design was used whereby the qualitative data collected using focus group work informed the Delphi survey questionnaire. Other types of mixed methods designs include explanatory sequential, parallel, and nested. [139] A possible alternative to the design used in the present study would have been an explanatory sequential design, whereby an international survey of trigeminal neuralgia stakeholders (patients, researchers and clinicians) on their preferences of treatment outcomes could have been done. This could have then been followed by one-to-one interviews of same stakeholders to discuss their choices in depth. Data synthesis would have been sequential.

A transparent and robust process of data collection, analysis, and interpretation was followed in the present study which has strengthened the conclusions drawn.

In the following chapters, a detailed description of each of the study's phases is presented.

CHAPTER 3 OUTCOMES IN TRIGEMINAL NEURALGIA A SYSTEMATIC REVIEW OF DOMAINS, DIMENSIONS AND MEASURES

3.1 OVERVIEW

Chapter 3 describes the results of a systematic review undertaken as the initial step in the development of the TN COS. Outcomes and outcome measures reported in studies evaluating medical and/surgical treatment for TN and the frequency of their use are summarised and discussed.

Work arising from this Chapter has been published in World Neurosurgery (open access, 2020) and the complete reference is in Appendix 5. Sections of this Chapter have been taken directly from the manuscript.

3.2 KNOWLEDGE GAP

Trigeminal Neuralgia remains one of the few neuropathic pain conditions for which multiple therapies, including medical and surgical, are available. However, the best treatment option is yet to be identified. The difficulty in defining what the most successful treatment for TN is relates to the fact that there are no clearly defined outcomes, therefore comparison between treatments is challenging. To improve comparison of treatments, clearly defined outcomes (what is assessed) and outcome measures (how to assess outcome magnitude) should be used.

There have been studies reporting on the use of outcome measures in individual TN treatments but there has not been a comprehensive review looking at all medical and surgical treatments published to date.

3.3 AIMS

The aims of this systematic review were:

1) To summarise all the treatment outcomes used in the TN literature,
2) To highlight the variability in the outcome reporting, and
3) To summarise the instruments used to measure those outcomes.

3.4 METHODS

A protocol for the systematic review was published in the International Prospective Registry of Systematic Reviews (PROSPERO) (Registration CRD42018118675, December 2018) and followed recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group. [140]

3.4.1 Search strategy

A literature search was conducted to include all trigeminal neuralgia studies where there was a medical and/or a surgical intervention with a view to capturing all treatment outcomes and the outcome measures used.

The searches were done electronically, with the help of a librarian, and by hand - MEDLINE (Ovid) (1946-October 2019 for medical treatment and 2008-October 2019 for surgical treatment), EMBASE (1947- October 2019 for medical treatment and 2008- October 2019 for surgical treatment), Cochrane Oral Health Group's Trials Register, CINAHL Plus with Full Text and PsycINFO. The search of surgical papers was restricted to studies published from 2008 onwards given that two systematic reviews had been published on surgical management of trigeminal neuralgia. [41, 141] Furthermore, international guidelines on the surgical management of TN[4] and a review of quality of reporting of surgical studies, which reviewed the literature up to 2008, [142] had also been published.

The search strategy for MEDLINE AND EMBASE can be found in Appendix 1.

3.4.2 Eligibility criteria

The inclusion criteria were:

1. Intervention studies with a cohort of patients diagnosed with trigeminal neuralgia,
2. Medical and/or surgical intervention,
3. TN cohort > or = 10 patients,
4. Subjects aged 18 years and over,
5. English language,
6. Full text available.

No discrimination was made concerning the study design, as the aim was to capture all the treatment outcomes and outcome measures published to date. Studies where

there were two or more cohorts (trigeminal neuralgia and hemifacial spasm, for example) were included but only data relevant to the TN cohort were evaluated.

3.4.3 Screening

The references were organised in EndNote X9 and duplicates removed. Initially, 25 study titles were piloted between two reviewers. The inter-rater agreement was 0.60. Following discussion and modification of the piloting sheet to include abstracts, the process was repeated with 50 further studies. The final Kappa's coefficient was 0.80.

The body of references was then screened on title and abstract; if no consensus was reached, a third reviewer made the final decision. Full texts, if available, were subsequently screened by three reviewers against eligibility criteria.

3.4.4 Data collection and synthesis

EPPI-Reviewer 4 software[143] was used to extract data from the final selected references. Data were extracted by three reviewers on TN classification (classical, idiopathic, and secondary to neurological disease, Burchiel classification, and unspecified), cohort type (prospective, retrospective, and unspecified), intervention (medical and/or surgical) and treatment outcomes (domain, dimension and instruments).

Data on outcome domains were captured according to the IMMPACT recommendations. [76] This review includes studies that precede those recommendations, as well as study designs other than clinical trials, but it was decided to use their guidance for a clear and standardised organisation of the results.

Treatment outcome measures were identified, and where available, data were collected on outcome measure instruments. The complete data extraction code can be found in Appendix 1.

3.4.5 Statistical analysis

Descriptive statistical analysis was performed to summarise the number of times outcomes and outcome measures were reported in the TN literature.

3.5 RESULTS

Four hundred and sixty-seven (n=467) papers were included in the final review and grouped according to TN classification, method of data collection, treatment intervention and treatment outcomes (domain, dimension and instruments/measures). Figure 3.1 illustrates the flow chart of references.

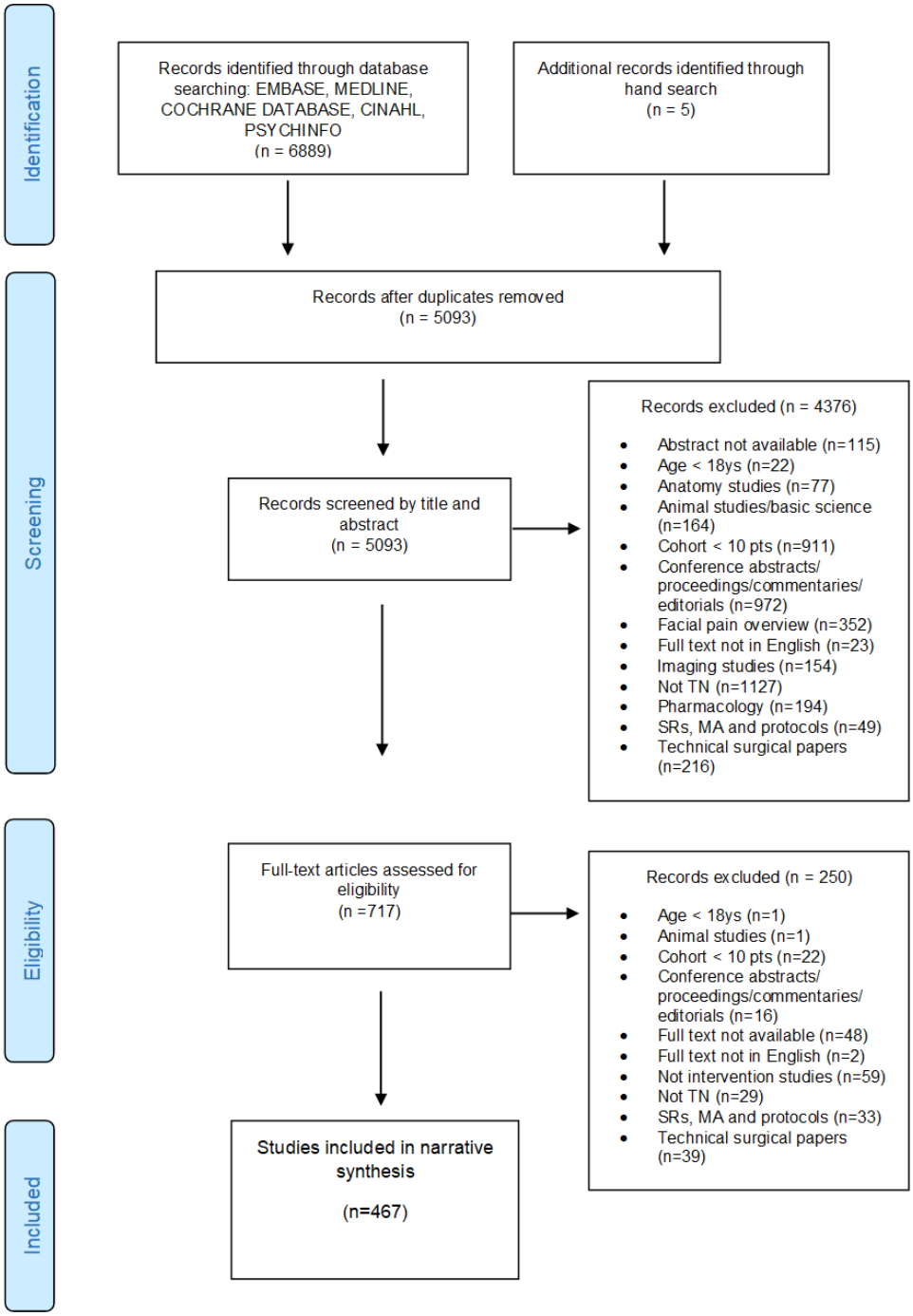

Figure 3.1 Systematic review - flow chart

3.5.1 TN Classification

Just under half of the papers (47%) described their TN cohort as classic, idiopathic, secondary to neurological disease or used the Burchiel classification. [144]

One hundred and twenty (n=120) studies did not specify the type of TN in their cohort and 47 others used a nomenclature which was not clearly defined, e.g. refractory TN, medically unresponsive TN, and recurrent TN after MVD.

3.5.2 Method of outcome data collection

More than half of the studies reviewed (n=254) collected their data retrospectively. Data were collected prospectively in 131 studies and 81 did not specify how their data were collected.

3.5.3 Intervention

Treatment interventions were divided into medical and surgical but data were not collected on the specific medical and surgical treatment modalities. The use of systemic and topical medicines and botulin toxin were included in medical management and all the ablative techniques, [41] neurosurgical procedures (MVD) and laser treatment in surgical management. The majority of studies reviewed were surgical papers (n=398) and a minority combined medical and surgical treatment (n=10).

3.5.3 Outcome domains, dimensions and measures

For systematisation and clarity, outcome data were organised and mapped to the IMMPACT outcome domain recommendations for clinical trials in chronic pain (Figure 3.2). [76] Only 42 of the 467 reviewed studies were published during or prior to 2003, predating the IMMPACT publication.

The IMMPACT Outcome Domains are as follows:

1. Pain
2. Physical functioning
3. Emotional functioning
4. Participant ratings of global improvement/satisfaction
5. Symptoms and adverse events
6. Participant disposition

With the exception of 8 papers, all studies used pain as an outcome domain (Figure 3.2 and Table 3.1). Symptoms and adverse events were also described in a high number of papers (n=386). However, the impact of treatment on physical and emotional functioning was significantly evaluated less, in 46 and 17 studies, respectively (Table 3.2). Of the 334 surgical studies that described adverse events, only 62 mentioned mortality rates. Participant disposition, i.e., how participants navigate through a study, was described in 16 studies (3%).

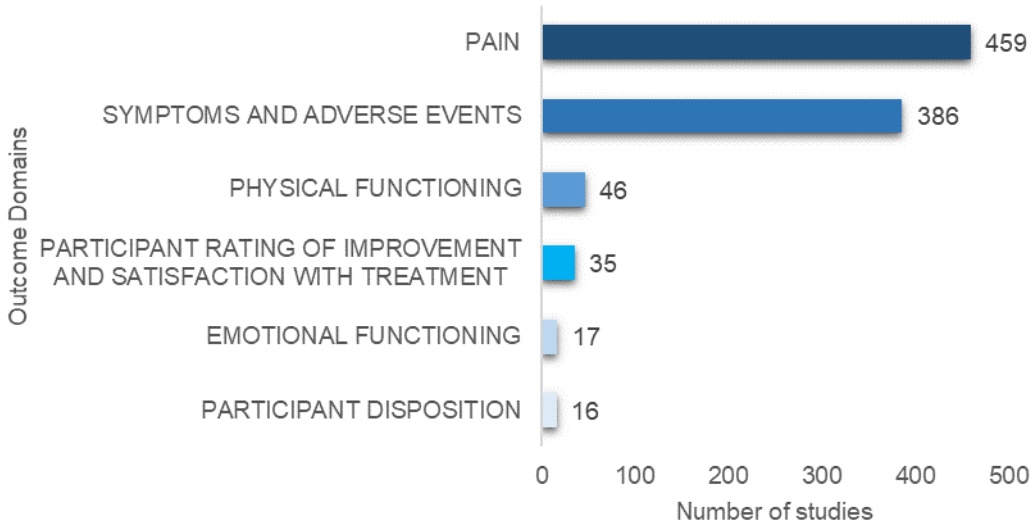

Figure 3.2 Number of studies divided according to IMMPACT recommendations on Outcome Domains

Pain

Pain Relief

Pain relief was used as an outcome dimension in the majority of studies (n=314). Ten different outcome measures were used for pain relief and 78 out of 314 (25%) studies did not use an outcome measure. The Barrow Neurology Institute Pain Intensity Scale (BNI) was the most used pain relief measure in 131 of studies (42%) followed by a Likert scale in 76 (24%) and the Visual Analogue Scale (VAS) in 18 (6%).

Pain Intensity

Pain intensity was used as a treatment outcome dimension in 193 of the 459 studies describing pain as an outcome domain. There were nine different measures used for pain intensity and eight studies did not use any. The VAS was the most commonly used measure in 85 studies followed by the BNI (n=45) and the use of qualitative pain descriptors (n=32).

Pain Frequency

Only 27 out of 459 studies (6%) used pain frequency as a treatment outcome dimension. The majority did not use an outcome measure (n=15) and ten indicated the use of a pain diary. One study used a pain vector diagram and another study used The Constant Face Pain Questionnaire.

Table 3.1 Pain dimensions and outcome measures identified in the systematic review

OUTCOME DIMENSION	OUTCOME MEASURE	REFERENCE NUMBER
PAIN RELIEF (314)	Barrow Neurology Institute Pain Intensity Scale (BNI)	145
	No Outcome Measure	35, 146-222
	Likert Scale	220, 223-297
	Visual Analogue Scale (VAS)	295, 298-314
	Numeric Rating Scale (NRS)	298, 315-319
	Modified BNI	320, 321
	Marseille Scale	322-324
	MVD Evaluation Score	325, 326
	Regis Classification	327, 328
	Burchiel Classification	329
	Other	330
PAIN INTENSITY (193)	Visual Analogue Scale (VAS)	147, 166, 170-172, 196, 220, 221, 242, 249, 297, 301, 302, 304, 305, 307-310, 312, 313, 331-394
	Barrow Neurology Institute Pain Intensity Scale (BNI)	196, 203, 211, 347, 363, 368-370, 395-431
	Qualitative Pain Descriptors	35, 152, 186, 188, 192, 193, 219, 297, 375, 398, 432-453
	Numeric Rating Scale (NRS)	25, 147, 236, 267, 279, 301, 307, 317-319, 437, 454-467
	Brief Pain Inventory (BPI)	25, 31, 38, 101, 314, 426, 468-473
	McGill Pain Questionnaire	38, 101, 215, 242, 279, 352, 364, 365, 397, 474
	No outcome measure	226, 293, 475-480
	Verbal Pain Scale (VPS)	215, 297, 372, 376, 434, 481, 482
	Verbal Numeric Pain Scale (VNPS)	35, 402, 483
	Other	330
PAIN FREQUENCY (27)	No outcome measure	161, 162, 208, 209, 357, 358, 362, 382, 459, 460, 471, 478, 484-486
	Pain diary	25, 35, 279, 293, 297, 312, 336, 385, 391, 487
	Pain vector diagram	481
	The Constant Face Pain Questionnaire	242

Physical functioning

Forty-six studies included at least one measure for evaluating physical functioning dimensions such as quality of life (n=34), daily activities (n=9), pain interference (n=4), ability to work (n=2) and disability (n=1). These are summarised in Table 3.2 with the references.

Quality of life

The most used instrument for assessing impact on quality of life was the 36-Item Short form Survey Instrument (SF-36) (n=14) followed by the EQ-5D (5-Question Quality of Life Instrument) (n=4), Sickness Impact Profile (n=2) and Brief Pain Inventory (BPI) (n=2).

The World Health Organization Quality of Life (WHOQOL-100) and 12-Item Short Form Health Survey (SF-12) were used in one study each. Of note, the BPI facial was used only once.

Two studies did not use an outcome measure and eight utilised a different measure (Quality of Life Impact Scale, 0-100 scale, Trigeminal Neuralgia Quality of Life Assessment Scale, Epilepsy Surgery Inventory-55, 10-point Quality of Life Scale, Wong Baker FACES scale and a 5-Point Scale).

Daily activities

Activity of daily living was the most commonly used instrument (n=4) followed by the Penn Facial Pain scale (n=1). One study did not use an outcome measure and four studies used different measures (Brief Fatigue Inventory, Karnofsky Performance Status Scale, Category Point Scale, Yes/No questions).

Pain interference

The only instrument used to evaluate pain interference was the BPI facial (n=4) which is the only instrument specific for facial pain.

Ability to work

Only two measures were used to evaluate ability to work, one study used a Likert scale and a second study used the Self Perceived Productivity Scale.

Disability

The Pain Disability Index was used in one study only.

Emotional functioning

Three dimensions were assessed in this domain: depression (n=5), anxiety (n=3), and catastrophising (n=1). Some studies combined anxiety and depression (n=12). Please refer to Table 3.2 for references.

Anxiety and Depression

The combination of anxiety and depression was evaluated by the use of Hospital Anxiety and Depression scale (HADs) in nine studies, and one study did not use an outcome measure. One other measure was found in two studies – the Research Diagnostic Criteria (RCD).

Depression

To evaluate depression alone, the Beck Depression Inventory (BDI) was used in three studies followed by the Hamilton Depression Scale (HDRS) (n=1) and the Patient Health Questionnaire-9 (PHQ9) (n=1).

Anxiety

To evaluate anxiety only two instruments were used, the Beck Anxiety Inventory (BAI) (n=2) and the Hamilton Anxiety Scale (HARS) (n=1).

Catastrophising

Only one study evaluated catastrophising, with the aid of the Pain Catastrophising Scale (PCS).

Table 3.2 Physical and emotional functioning domains and outcome measures identified in the systematic review

REFERENCE	PHYSICAL FUNCTION (46)	EMOTIONAL FUNCTION (17)
Azar (2009) [488]	Quality of life • SF-36	
Bohman (2014) [468]	Pain interference • BPI facial	
Campos (2011) [338]	Quality of life • Other – Quality of life impact scale	
Chao (2012) [469]	• Daily activities • Other: Brief Fatigue Inventory	
Cheng (2017) [341]		Anxiety • Beck Anxiety Inventory (BAI) Depression • Beck Depression Inventory (BDI)
Di Stani (2015) [471]	Quality of life • SF-36	Depression • Beck Depression Inventory (BDI)
Ding (2016) [455]	Quality of life • WHOQOL-100	
Gagliardi (2018) [324]	Quality of life • SF-36 Daily activities • Activity of Daily living • Other: Karnofksy performance scale	
Gao (2019) [394]	Quality of life • SF-36	
Huang (2010) [172]	Quality of life • Other: 0-100 scale	
Ichida (2015) [349]		Anxiety and Depression Other
Ichida (2017) [350]		• Anxiety and Depression Other
Jafree (2018) [489]	Quality of life • SF-12	Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS)

Jorns (2009) [352]	Quality of life • SF-36 • BPI	Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS)
Knafo (2009) [262]	Quality of life • Other: Trigeminal neuralgia quality of life assessment scale	
Ko (2015) [490]	Pain interference • BPI facial	
Kotecha (2017) [491]	Quality of life • EQ-5D	Depression • Patient Health Questionnaire-9 (PHQ9)
Lai (2011) [298]	Quality of life • No outcome measure	
Lee (2015) [473]	Pain interference • BPI facial	
Lee (2017) [492]	Daily activities • Penn Facial Pain Scale	
Lemos (2008) [357]	Quality of life • Sickness Impact Profile	
Lemos (2011) [459]	Quality of life • Sickness Impact Profile	Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS)
Li (2012) [267]	Quality of life • EQ-5D	
Liang (2017) [461]	Quality of life • Other: 0-100 scale	
Little (2008) [493]	Pain interference • BPI facial	
Little (2009) [494]	Quality of life • BPI	
Lunardi (1997) [437]	Daily activities • Activity of Daily living	
Mitsikostas (2010) [362]	Quality of life • SF-36	Anxiety • Hamilton Anxiety Scale (HARS) Depression • Hamilton Depression (HDRS)
Mousavi (2016) [412]		Anxiety and Depression • No outcome measure

Obermueller (2018) [414]	Quality of life • EQ-5D Ability to work • Likert scale	
Pan (2010) [363]	Quality of life • SF-36	
Perez (2009) [364]	Quality of life • EQ-5D Disability • Pain disability index	Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS)
Perez (2009) [365]	Ability to work • Self perceived productivity scale Daily activities • Activity of Daily living	
Reddy (2013) [369]	Quality of life • SF-36	
Reddy (2014) [368]	Quality of life • SF-36	
Regis (2006) [370]	Quality of life • Other: Epilepsy Surgery Inventory-55	
Rustagi (2014) [279]	Daily activities • Activity of Daily living	
Sekula (2010) [283]	Quality of life • No outcome measure	
Shehata (2013) [373]	Quality of life • Other: 10-point quality of life scale	
Shibahashi (2013) [449]	Quality of life • SF-36	
Singla (2011) [376]	Daily activities • Other: Category point scale (CPS) or functional outcome scale for main daily activities	
Solaro (2000) [477]	Daily activities • No outcome measure	
Tang (2016) [381]		Anxiety • Beck Anxiety Inventory (BAI) Depression • Beck Depression Inventory (BDI)

Tentolouris-Piperas (2018) [495]	Quality of life • BPI facial	Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS)
Yao (2016) [496]	Quality of life • SF-36	
Yao (2016) [389]	Quality of life • SF-36	
Young (2013) [330]	Quality of life • Other: Wong Baker FACES scale	
Zakrzewska (1997) [293]	Daily activities • Other: yes/no question	
Zakrzewska (1999) [474]		Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS)
Zakrzewska (2002) [215]	Quality of life • Other: 5 point scale	Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS)
Zakrzewska (2005) [38]	Quality of life • SF-36	Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS)
Zakrzewska (2017) [101]		Anxiety and Depression • Hospital Anxiety and Depression Scale (HADS) Catastrophising • Pain Catastrophing Scale (PCS)
Zuniga (2013) [393]	Quality of life • SF-36	

Satisfaction with treatment

Only 35 studies (7%) reported on patient ratings of improvement and satisfaction with treatment.

The majority of studies (n=17) used a Likert Scale to rate their patient satisfaction with treatment whereas two studies used a Patient Satisfaction Scale and one other a VAS scale. Nine studies used the Patient Global Impression of Change (PGIC) to rate change with treatment. Three studies did not use an outcome measure and four studies used four other outcome measures (QUASU - Satisfaction with Treatment and Medical Team; Satisfaction Survey; The Patient Global Rating of Efficacy and Safety and The Wong Baker FACES scale).

Adverse events

Data on adverse events and side effects were collected in 83% of the studies.

Of the 59 medical studies, 85% described side effects. Outcome measures were used in only three studies – The Liverpool Adverse Event Profile (n=2) and the A-B Neuropsychological Assessment Schedule (ABNAS) (n=1).

Of the surgical studies group, side effects and adverse events were collected in 334 (84%). The most reported side effect was numbness (n=220) and the Barrow Neurology Institute Numbness Scale was administered in 62 studies. A Likert scale was used once to assess degree of numbness. One other surgical study used the Landriel Ibanez classification, but the majority of studies limited their reporting to the passive description of the cohort side effects opposed to using an instrument to collect the data.

Patient disposition

Patient disposition is not considered a treatment outcome. This domain refers to the patient navigating through a study, and is often presented in a flow diagram.

Guidance on reporting for the different types of studies has been published by the EQUATOR Network (Enhancing the QUAlity and Transparency Of health Research) (https://www.equator-network.org/) and endorsed by medical and surgical journals. [142] It has been accepted that the reporting of the patient progression in clinical trials should be illustrated by a CONSORT diagram (Consolidated Standards of Reporting Trials) [87] and, in the case of observational trials, the STROBE statement (Strengthening the Reporting of Observational studies in Epidemiology) should be followed. [497]

In this review, 16 studies were identified in which there was information about patient progression – CONSORT diagram (n=4), STROBE reporting (n=5) and seven illustrated their information with a diagram but did not follow any specific guidance.

3.6 DISCUSSION

Using a systematic approach, this review provides a summary of the outcomes and outcome measures that have been used in the medical and surgical treatment of TN to date, performed by clinicians from varied backgrounds, and it highlights the variability in the methodology of studies and choice of outcome measures employed.

3.6.1 Pain - outcome dimensions and outcome measures

The degree of pain relief as well as the level of pain intensity have been the most commonly used dimensions in chronic pain studies. [498] [499] Similar to what others have found in the TN surgical literature, [41, 141, 142] the most common pain dimension reported was pain relief. TN is an episodic pain, it is interesting to see that little attention is given to this specific characteristic. To date, no instruments have been designed to capture the effects of treatment on the number and frequency of TN attacks. Degn and Brennum have attempted to capture this data in a cohort of patients undergoing glycerol injection, microvascular decompression and rhizotomy, by plotting pain intensity (Verbal Numerical Rating Scale - VNRS) with frequency of daily pain per month. [481] Their data were used to design a pain vector diagram to illustrate, in a composite outcome, the effects of treatment. Another temporal aspect of pain is duration of pain free status over time which has been illustrated in the literature with Kaplan Meier survival curves. [142] It is almost certain that patients would value information about which treatment provides absence of pain for the longest period of time and it might be that plotting pain relief outcome data over time is the correct way of doing it, however, rigorous reporting of follow up times are essential for data accuracy.

The VAS and BNI intensity scales are the most used tools to capture data on pain intensity. Both scales were also utilised to retrieve information on pain relief. Given that VAS is a single item scale and BNI is a composite scale, it is not possible to compare data captured by these instruments, especially as they are measuring different pain dimensions and the BNI includes data on medication use. Despite their wide utilisation in TN, neither the VAS nor the BNI have been validated for their use in TN cohorts. [41, 500 501] It is not clear if patients complete the scales or whether the data are retrieved from the medical records.

Finally, it is important to stress that the use of outcomes that are designed specifically for a single study, or which have been modified and derived from other instruments, for example modified BNI[320, 321] and have not been validated for TN are neither reliable nor reproducible and comparison of study results is flawed.

3.6.2 Data collection method

The retrospective collection of data, specifically, the interviewing of patients, months or years after their treatments were done, raises the question of recall bias and it can be influenced, for example, by severity of pain at time of recall. [502]

Of note, in one of the studies, family members of deceased patients were contacted to obtain information about their condition. [236] The experience of pain is a very personal one and it is unreasonable to expect that others can provide information, except if stated early on, that the outcome collected is not patient reported. If the information sought is related to effects of treatment on someone's level of pain, then the patient is the only valid source of information. [503]

3.6.3 Domains other than pain

There has been extensive research highlighting the impact of chronic pain in mood and quality of life. [504] Tölle and colleagues, [505] and Zakrzewska *et al*[101] described the high impact of TN pain on activities of daily living as well as emotional functioning but the reporting of TN impact on QOL has been sparse. [506] None of the eight different instruments used for emotional functioning have been validated for TN. The BPI facial has been validated in a cohort of TN patients, [507] but its uptake, in studies published since 2010 and included in this review, is low, being used in four studies to assess pain interference [468, 473, 490, 493] and in one to assess impact on quality of life. [495] Interpreting the effects of TN on the emotional and physical health will also depend on the appropriateness of these instruments for their use in a TN cohort.

The reporting of side effects should go beyond a narrative list and incorporate how individual side effects might affect patients' QOL or what the impact on daily living is. As illustrated by Akram *et al*, [142] the side effects of treatment might impact more on a patient's QOL than the pain itself.

There might be a few practical explanations for the poor reporting on domains other than pain. First, reporting on multiple outcome domains would require more comprehensive questionnaire(s) that could be a burden to patients, risking a poor response rate and validity of results. Secondly, time might be a limiting factor for researchers who need to administer, collect and analyse all the data. Patients may not be made aware of their relevance and so not complete them. Finally, although attempts have been made to improve reporting of outcomes in studies on TN, journal editors have not insisted on more comprehensive reporting. [142]

3.6.4 Limitations

The inclusion of a large number of studies to summarise information on outcomes and outcome measures in the treatment of TN created a heterogeneous data set which was challenging to organise. Although the content of this Chapter fulfils most criteria for a well conducted systematic review, the included studies were not appraised on their scientific rigour. One of our aims was to truly capture the diversity of outcomes and outcome measures which had been published in the literature.

Due to the volume of results, data extraction on outcomes was limited to identifying the outcome measure instrument used and for the majority of the studies information concerning the timing and method of questionnaire administration was not retrieved. Finally, the search included English literature only and this has contributed to language bias. Although searches limited to English language are usually done due to lack of resources (lack of available team members who can either interpret and/or translate papers), financial and time limits, it is important to acknowledge that relevant research published in other languages might have been left out. One should not assume that because 467 English language studies were included for analysis, important outcomes have not been missed. This study was looking at outcomes used in TN studies, which traditionally have been chosen by clinicians and researchers. Health care professionals might investigate and deliver care differently to meet the needs of people from different cultures/countries. There is evidence supporting the influence of culture in pain related factors, for example, the communication of pain, beliefs about pain, ability to cope with pain and pain catastrophising. [508] Sharma and colleagues illustrate the differences in pain communication with an example from the Asian cultures where, in some countries, people tend to avoid talking about pain. [508]

Furthermore, education levels might influence how someone appraises information about pain, but equally, access to information which might be inaccurate might influence an individual to change their behaviour towards pain, often avoiding movement to prevent further damage or increased pain. In contrast, the example given by Sharma and colleagues while trying to investigate the prevalence of musculoskeletal pain in rural Nepal illustrates that there were no reports of lower back pain as the population believes that lower back pain is part of the normal aging process and consequently do not seek medical care. [508]

3.7 SUMMARY

There is a huge variability in the use and reporting of treatment outcomes in the TN literature. Multiple questionnaires have been used to assess these outcomes, however, have these been tested to be used in TN research? Chapter 4, which outlines the results of a systematic review of the psychometric properties of questionnaires used in TN, answers this question.

CHAPTER 4 PATIENT REPORTED OUTCOMES IN TRIGEMINAL NEURALGIA AND THEIR PSYCHOMETRIC PROPERTIES – A SYSTEMATIC REVIEW

4.1 OVERVIEW

The indiscriminate use of outcome measures, as outlined in Chapter 3, can influence the results and therefore, conclusions of research studies. To truly understand the impact of an intervention, many steps must be followed at the research design stage, including the correct choice of questionnaires for the assessment of outcomes. This Chapter describes and discusses the results of a systematic review looking at questionnaires used in TN.

Work arising from this Chapter has been published in The European Journal of Pain (open access, 2021) and the complete reference is in Appendix 5. Sections of this Chapter have been taken directly from the manuscript.

4.2 KNOWLEDGE GAP

Currently, there is a lack of guidance on what the most appropriate instruments to be used in TN studies are. As in many other health conditions, most constructs are subjective such as pain (intensity, frequency, interference and health related quality of life (HRQOL) for example, and given this subjectivity, the direct reporting from the patient is of utmost importance. Patient reported outcome measures (PROMs) are questionnaires or forms completed by the patients about their health without interpretation by a clinician or researcher. [509] A patient reported outcome (PRO) can also be a record obtained by direct questioning or interviewing of the patient.

PROMs should be chosen on their psychometric performance in the studied population to allow for comparison of study results. There have been repeated calls that measures of patient-reported outcome assessment should be standardised and validated, exemplified by the Big Data for Better Outcomes comprehensive European research programme. [5,10]

As a minimum, a questionnaire should be validated to be used in the target population for the outcome of interest, in a specific context, and should therefore be relevant, comprehensive and comprehensible – content validity. [65] The instruments should also demonstrate adequate structural validity (the instrument scores reflect the construct to be measured), reliability (the scores of the instrument do not change when patients are stable, despite possible changes in the timing of the measurement and the instrument rater) and responsiveness (if there is a change in the construct of interest, for example due to a new treatment, the instrument is able to detect it). Additionally, the questionnaires should also be easy to interpret and be feasible to use without causing excessive burden on patients or clinicians. [69]

4.3 AIMS

The aim of this systematic review was to summarise and evaluate the psychometric properties of outcome measures that have been developed or adapted for TN patients undergoing treatment and to make recommendations for their use in future studies.

4.4 METHODS

The methodology adopted for this systematic review follows guidance from COSMIN[69] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-statement). [511]

A protocol was prepared and registered in PROSPERO (CRD42020185914, 1 July 2020) before starting the systematic review process.

4.4.1 Literature search

A systematic search was performed in MEDLINE (Pubmed) (1966-2020), EMBASE (Ovid) (1980-2020), CINAHL Plus with Full Text (1937-2020), PsycINFO (Ovid) and Health and Psychosocial Instruments (1985-2020).

The search was designed to identify all studies where there was (a) development, evaluation and/or validation of measurement properties of (b) patient reported outcome measures in (c) adult trigeminal neuralgia patient cohorts. A published and validated search filter designed for Medline was used, with a high sensitivity for retrieving results on measurement properties studies. [512] This filter was then adapted for the search in EMBASE, CINAHL and PsycINFO. The search on the Health and Psychosocial Instruments database was limited to the target population, i.e., trigeminal neuralgia.

The full search strategy can be found in Appendix 2.

4.4.2 Eligibility criteria

Studies were included with a TN patient cohort >18 years of age, which aimed to evaluate and/or validate measurement properties of patient reported outcome measure (s), develop a patient reported outcome or evaluate the interpretability of a patient reported outcome. Only full text articles reported in English were included. Studies, which described the use of clinician reported outcomes only were excluded. In addition, conference abstracts, editorials, conference proceedings were also excluded. A choice was made not to search for any specific PROM or specify domains or dimensions of the PROM as it was anticipated that the search would not yield many results.

4.4.3 Study records

The records identified were transferred to EndNote X9.2 (Clarivate Analytics) and duplicates removed. Two researchers independently screened the records by title and abstract. Three researchers independently screened the records based on full text. Disagreements were resolved with discussion. Once records were identified as eligible to be included, data were extracted (see below).

4.4.4 Measurement properties

Data Extraction

Data were extracted by one author using a preselected form based on those recommended by COSMIN [513] on both study details (study design, sample size, gender, age, TN classification and type of treatment) and PROM description (PROM,

construct, mode of administration and psychometric properties under study). A second author confirmed the data extracted for accuracy. There were no disagreements.

The measurement properties under study were labelled according to the guidance provided by COSMIN. [69] This included evidence of the assessment of the following measurement properties: content validity, internal structure (structural validity, internal consistency) and the remaining properties (test-retest reliability, measurement error, criterion validity, construct validity, responsiveness). Content validity, which is defined by COSMIN as the degree to which the content of a PROM is an adequate reflection of the construct to be measured, is considered the most important measurement property.

The assessment of content validity was based on guidance from a recent Delphi study[65], which recommends that well-designed PROM development studies should be taken into consideration in the assessment of content validity. Development studies which use qualitative research methods allow for direct patient input in different stages, such as concept elicitation, item generation, comprehensibility, and comprehensiveness. [514]

Assessment of the methodological quality of the studies

Two reviewers independently assessed the included studies to evaluate their methodological quality and consensus was reached during an online meeting. The methodological assessment was done in three steps as recommended by COSMIN.

In Step 1, the methodological quality was assessed using the risk of bias checklist. [69] This checklist consists of a table which outlines all the measurement properties as well as the PROM development study characteristics against quality standards.

There are four possible scores for each standard: “very good”, “adequate”, “doubtful” or “inadequate”. The overall score for the methodological quality of the study was taken by using the “the worst score counts” principle. Details of this can be found in Appendix 2.

In Step 2, criteria for good measurement properties were applied by using the following quality ratings: “sufficient” (+), “insufficient” (-) or “indeterminate” (?) (see Table 4.1[513] for details). At this stage, the results of different studies, if consistent, are pooled together for assessment of the overall quality rating of each PROM as “sufficient” (+), “insufficient” (-), “inconsistent” (±) or “indeterminate” (?).

Finally, in Step 3, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) modified method was used to grade the overall quality of the evidence collected of each measurement property as “high”, “moderate”, “low”, or “very low”. [65, 69]

Table 4.1 Classification criteria for measurement properties

Measurement property	Rating	Criteria
Structural validity	+	**CTT** CFA: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08
	+	**IRT/Rasch** No violation of unidimensionality: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08 *AND* no violation of local independence: residual correlations among the items after controlling for the dominant factor < 0.20 OR Q3's < 0.37 *AND* no violation of monotonicity: adequate looking graphs OR item scalability > 0.30 *AND* adequate model fit IRT: $\chi^2 > 0.001$ Rasch: infit and outfit mean squares ≥ 0.5 and ≤ 1.5 OR Z-standardized values > −2 and < 2
	?	CTT: not all information for '+' reported IRT/Rasch: model fit not reported
	−	Criteria for '+' not met
Internal consistency	+	At least low evidence for sufficient structural validity AND Cronbach's alpha(s) ≥ 0.70 for each unidimensional scale or subscale
	?	Criteria for "At least low evidence for sufficient structural validity" not met
	−	At least low evidence for sufficient structural validity AND Cronbach's alpha(s) < 0.70 for each unidimensional scale or subscale
Reliability	+	ICC or weighted Kappa ≥ 0.70
	?	ICC or weighted Kappa not reported
	−	ICC or weighted Kappa < 0.70
Measurement error	+	SDC or LoA < MIC
	?	MIC not defined
	−	SDC or LoA > MIC
Criterion validity	+	Correlation with gold standard ≥ 0.70 OR AUC ≥ 0.70

Measurement property	Rating	Criteria
	?	Not all information for '+' reported
	−	Correlation with gold standard < 0.70 OR AUC < 0.70
Responsiveness	+	The result is in accordance with the hypothesis OR AUC ≥ 0.70
	?	No hypothesis defined (by the review team)
	−	The result is not in accordance with the hypothesis OR AUC < 0.70

Adapted from: COSMIN guideline for systematic reviews of patient-reported outcome measures [69]

CTT= classical test theory, CFA= confirmatory factor analysis; CFI= comparative fit index, TLI=Tucker-Lewis index

RMSEA=root mean square error of approximation, SRMR= standardized root mean residuals

IRT=item response theory, ICC= intraclass correlation coefficient, SDC= small detectable change; LoA=limits of agreement, MIC=minimal important change; AUC= Area under the curve

"+" = positive rating, "-" = negative rating,"?" = indeterminate rating

4.5 RESULTS

The search identified 549 titles. After 141 duplicates were removed, 408 abstracts were screened. Of these, 18 full text articles were screened but only six were included for the final analysis. Figure 4.1 displays the study records flowchart, with documented reasons for exclusion in different phases of the screening process.

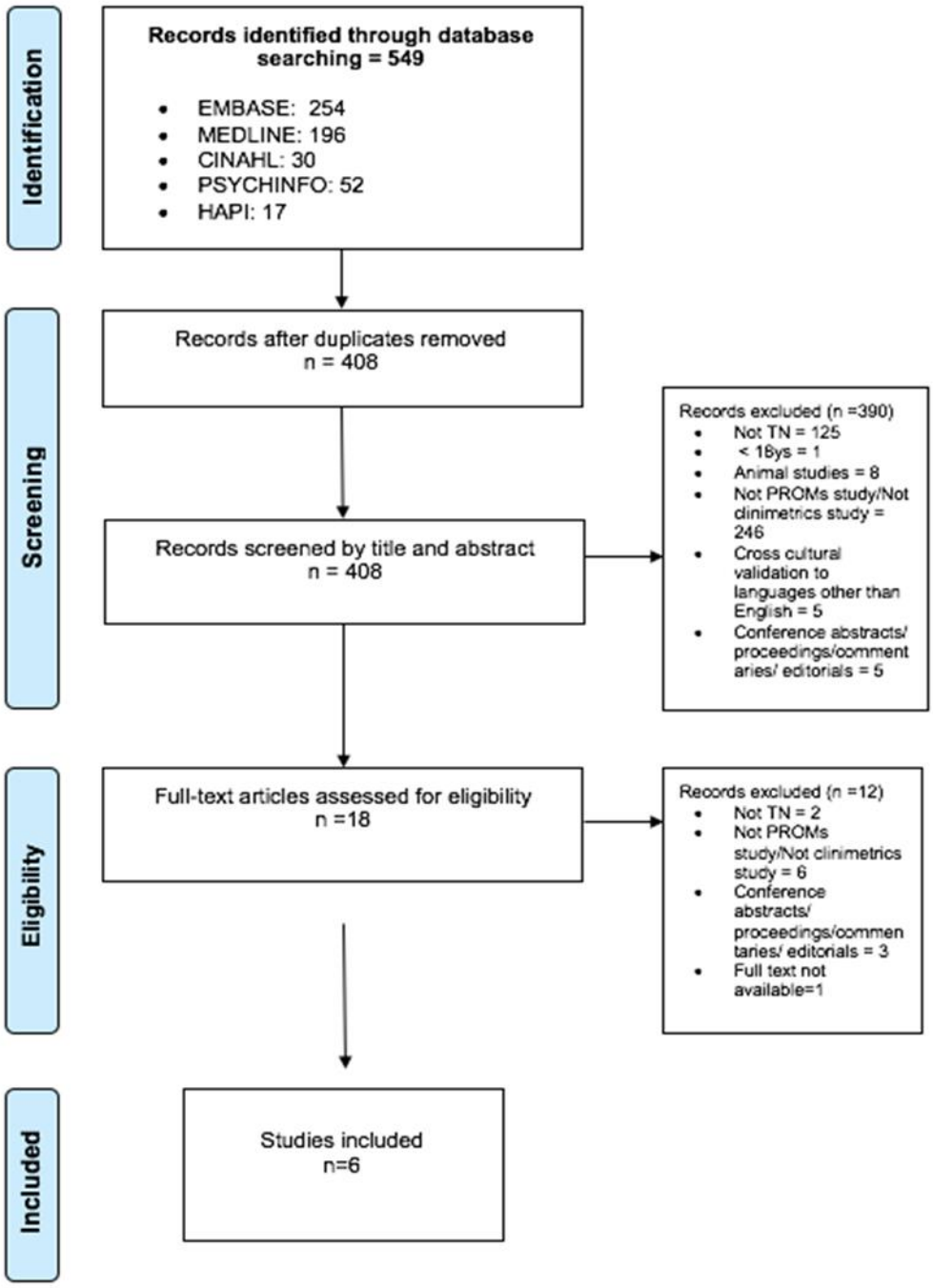

Figure 4.1 Flowchart of search strategy results.

A total of five PROMs were identified in the six articles: BPI-F – Brief Pain Inventory Facial[507], VAS – Visual Analogue Scale[515, 516], BNI-PS – Barrow Neurology Institute Pain Scale[515, 516], Penn Facial Pain Scale Revised [517] and the Trigeminal Neuralgia Quality of Life Score. [518] Please see Table 4.2 for the characteristics of the included studies.

4.5.1 Brief Pain Inventory Facial (BPI-Facial)

The BPI-Facial[507] was intended to be designed as a subscale adaptation of the Brief Pain Inventory[519] to allow for the inclusion of seven extra questions specific to interference of pain related to the face. It included, for example, questions about interference of pain on eating a meal or on smiling, laughing or talking. The BPI was originally developed to be used in cancer pain as a pain intensity (severity) and pain interference tool. [519] Since its development, it has been widely used in different pain conditions, translated into different languages and validated to be used in different clinical and research contexts. The pain intensity subscale consists of four items rated on an eleven-point scale (0-10) with anchors “no pain” and “pain as bad as you can imagine”. The pain interference subscale consists of seven items rated on an 11-point scale (0-10) with anchors “does not interfere” and “completely interferes”. The BPI-F subscale on interference (face) consisted of seven new items rated on an 11-point scale (0-10) with anchors “does not interfere” and “completely interferes”.

One study presented data on the BPI-F subscale development, structural validity and internal consistency[507] and one study presented data on the scale’s interpretability. [520]

Table 4.2 Details of the included studies

Reference	Study design	Sample size (%females)	TN Classification	Treatment	PROM	Construct	Mode of administration	Psychometric properties evaluated*
Lee *et al*, 2010	Cross sectional	156 (63%)	Burchiel Type 1 classic TN or Burchiel Type 2	Unclear	BPI – F	Pain interference facial	Self-completed by patient	Subscale development [a] Content validity Structural validity Internal consistency
Reddy et al, 2013	Prospective cohort study	60 (78%)	Classic trigeminal neuralgia	MVD	VAS BNI-PS	Pain intensity	Face to face interviews base line and 2 years FUP	Interpretability [a]
Reddy et al, 2014	Prospective cohort study	43 (67%)	Based on the International Headache Society Classification, no further details	Percutaneous Stereotactic Radiofrequency	VAS BNI-PS	Pain intensity	Face to face interviews at base line and 2 years follow up	Interpretability [a]
Sandhu et al, 2015	Retrospective cohort study	234 (62%)	Burchiel Type 1 classic TN or Burchiel Type 2	Neurosurgery	BPI - F	Pain intensity Pain interference general Pain interference facial	Self-completed by the patient at initial visit and 30 days after treatment	Interpretability [a]
Symonds et al, 2018	Semi-structured interviews	20 (85%)	Unclear	Medical treatment	Penn Facial Pain Scale Revised	Pain interference on HRQOL and daily functioning	Self-completed by the patient	Subscale development [a] Content validity
Luo et al, 2019	Not described	298 (not available)	Primary TN	Radiofrequency thermocoagulation	TN QOLS	Quality of life	Self-completed by the patient	Subscale development [a] Content validity Criterion validity Structural validity Internal consistency Responsiveness

Abbreviations: MVD=microvascular decompression, PROM=patient reported outcome measure, BPI-F=brief pain inventory facial, VAS=visual analogue scale

BNI-PS=Barrow Neurological Institute Pain Scale, TN QOLS=Trigeminal Neuralgia Quality of Life Score

[a]Subscale development and interpretability are not considered measurement properties but the former can be used to aid in content validity assessment and the latter should be assessed when the other measurement properties fulfil criteria of quality.

Validity

Subscale development and content validity

The subscale development study was of doubtful quality as it is unclear if patients were asked about the comprehensibility and comprehensiveness of the PROM.

In the absence of content validity studies for this subscale, the content validity rating was based on the development study and on the reviewer's ratings which provided low evidence for inconsistent findings.

Internal structure

Structural validity and internal consistency

One study of adequate quality assessed the structural validity and internal consistency of the BPI-Facial. [521] However, it was not clear if the items of the subscale were based on a reflective or formative model. It was assumed that the items of the "pain interference facial" construct were based on a reflective model drawn from the literature and consultation of experts in the field. The authors of the study hypothesised that the BPI-Facial could be a two or three factor questionnaire and conducted a principal factor analysis with varimax rotated factor. Three factors with eigenvalues >1 (interference facial 5.4/ interference general 4.3 / pain intensity 2.3) were identified and confirmed with a scree plot. The three factors explained 97.6% of the variance of the instrument. A cut-off >0.4 was used for the loading values suggesting a high correlation of the items with the domain. The pain interference facial factor loading varied from 0.73 (impact of pain on eating) to 0.87 (impact of pain on brushing and on smiling). These findings suggest moderate evidence for sufficient unidimensionality of the pain interference subscale.

The internal consistency of the pain interference facial subscale was 0.95 calculated using Cronbach's α. Taking into consideration the moderate evidence for sufficient structural validity and Cronbach's α > than 0.70, there is moderate evidence for sufficient internal consistency.

Interpretability

According to COSMIN, interpretability is not a measurement property, rather a feature to be taken into consideration when choosing an instrument as it attributes meaning to an instrument's single score or change in scores. [69] One study assessed the interpretability of the BPI-Facial by calculating the minimum clinically important difference (MCID) with two anchor-based methods: mean change score and receiver operating curve (ROC) analysis. [520] The patient global impression of change scale (PGIC) was the anchor used which patients completed on follow up choosing one of the following options: very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse. The mean change score was calculated for one subgroup only ("much improved" n=47) and percentages of change in scores calculated. Patients needed a 30 and 44% improvement in pain intensity worst and average respectively to choose the "much improved option" and a higher percentage change of scores for interference general (54%) and interference facial (63%). Cut-off points were calculated for the domains pain intensity (worse and average), interference general and interference facial for three different models based on the distribution of patients on the PGCI scale – very much improved; much and very much improved, minimally, much and very much improved.

The model chosen for analysis was the one which included much and very much improved patients (n=159). Sensitivity and specificity were calculated. For worst and average pain intensity and interference general, sensitivity was 65.5%, 65.7% and 68.3% respectively, which indicates that there is a moderate percentage of false positive misclassifications. Specificity was higher for all the domains ranging from 71.9% (interference facial) - 90.7% (worst pain intensity).

4.5.2 Barrow Neurology Institute Pain Scale (BNI-PS)

The BNI-PS was used for the first time in a study designed to assess the efficacy of gamma knife radiosurgery in a cohort of TN patients and, according to the authors, it is a pain intensity scale [522] but requirement for medication is also taken into account. The scoring options outlined on that initial study are: “I – No trigeminal pain, no medication”, “II – Occasional pain, not requiring medication”, “III – Some pain, adequately controlled with medications”, “IV – Some pain, not adequately controlled with medication” and “V – Severe pain/no relief. For a more comprehensive description of this questionnaire, please see the review by Sandhu and Lee. [523]

There is no evidence in the literature of any studies that attest or attempt to validate the BNI-PS for its use in trigeminal neuralgia studies. The author of the study where it was used for the first time was contacted by email for clarification, but they never replied. It is not clear if patients complete it or if the data are taken from medical records.

Interpretability

Two of the included studies were designed to determine the interpretability of the Barrow Neurology Institute Pain Scale (BNI-PS) [515, 516] but the authors of this review agreed that the interpretability of the questionnaire has no significance without evidence of its measurement properties.

4.5.3 Visual Analogue Scale (VAS)

Two of the included studies were designed to determine the interpretability of the VAS[515, 516].The visual analogue scale (VAS) is a pain intensity scale widely used [524]. It is an unidimensional continuous scale which scores pain intensity on a 10-cm (100mm) horizontal or vertical line. [525] There have been some criticisms of the feasibility of using VAS as a pain intensity measurement, related with the difficulties that the elderly or those with cognitive and physical impairment have in completing it which might result in missing data. For this reason, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends the numerical rating scale (NRS) for the assessment of pain intensity in clinical trials of chronic pain. [526]

Interpretability

The studies which aimed to determine the interpretability of the BNI-PS also set out to determine the interpretability of the VAS. Given the absence of VAS psychometric studies within the TN literature, its interpretability was not described.

4.5.4 Penn Facial Pain Scale – Revised (Penn-FPS-R)

The Penn Facial Pain Scale Revised was developed with the intent to be a revised version of the Penn Facial Pain Scale which was in turn previously called the BPI – Facial (please see description above), due to the absence of content validity properties.[517] Similarly, to the BPI-Facial and to the Penn Facial Pain scale, the Penn-FPS-Revised was designed to capture details on general and TN-specific pain interference. The original BPI-Facial and the Penn Facial Pain Scale included items related to pain interference on activities of daily living specific to patients living with TN such as “eating a meal”, “touching one’s face”, “brushing or flossing one’s teeth”, “smiling or laughing”, “talking”, “opening one’s mouth widely”, and “eating hard food like apples”.[517] These 7 items were rated on an eleven-point scale (0-10) with anchors “does not interfere” and “completely interferes”. In a qualitative study with TN patients[517], the item “eating hard food like apples” was removed and replaced by “biting or chewing” and two new items were added, “self-care” and “activities affected by temperature changes”. Furthermore, the original BPI Facial included 7 items of general pain interference such as impact of pain on “walking ability”, “normal work”, “sleep” and “enjoyment of life”, which the participants of this study decided were not relevant in the context of their disease. The finalised version of Penn Facial Pain Scale Revised is a questionnaire which includes 12-items.[517]

Validity

Subscale development and content validity

The subscale development study was of adequate quality. [517] In the absence of content validity studies with new patient cohorts, the content validity rating was based on the development study and on the reviewer's ratings which provided moderate quality evidence for sufficient content validity.

4.5.5 Trigeminal Neuralgia Quality of Life Score (TN QOLS)

One study was identified, which aimed to develop a TN specific quality of life subscale for the Quality of Life Instruments for Chronic Diseases (QLICD), which is a questionnaire developed to assess quality of life in Chinese populations with chronic diseases. [527] It consists of a general subscale (QLICD-GM) and disease specific subscales, which exist for hypertension, irritable bowel syndrome and chronic obstructive pulmonary disease, to name a few. [528] Despite the use of qualitative methods in the development of the QLICD-GM, patients were not involved nor were they asked about the contents of the questionnaire; therefore, it cannot be assumed that this general subscale has content validity.

Validity

Subscale development and content validity

One study aimed to develop and confirm content validity for the TN specific QOL subscale of the QLICD. [518] The questionnaire development was of doubtful quality, and no details could be retrieved on the extent of patient involvement.

Content validity ratings were based on the development study and on the reviewer's ratings as there was no indication of the subscale being tested on a new cohort. The reviewers deemed content validity insufficient. This resulted in very low quality for insufficient content validity.

Criterion validity

Criterion validity was described but not assessed in this review, as there are no gold standard questionnaires to assess quality of life in trigeminal neuralgia cohorts.

Internal structure

Structural validity and internal consistency

The authors used factor analysis to determine the structural validity of the TN QOLS in a study of doubtful quality. Four factors were identified which accounted for 65.82% of variance. Due to the lack of further information on the factor analysis results (for example, there was no information on the eigenvalues, nor was there information on the cut off value for the factor loadings) there was very low evidence for insufficient structure validity. Cronbach's α was calculated for internal consistency, and results were >0.70 for each of the four factors, however, due very low evidence for insufficient structural validity, internal consistency was deemed indeterminate.

Responsiveness

It is unclear how responsiveness was determined on a study of inadequate quality as there was no evidence of hypothesis testing with a comparator outcome measure. Responsiveness of TN QOLS was insufficient based on very low-quality evidence.

4.6 DISCUSSION

This systematic review is the first to use COSMIN guidance to evaluate the measurement properties of PROMs used in patients with TN.

The review identified six studies, in which five different PROMs were used to assess pain intensity, pain interference on activities (general and facial), pain interference on quality of life and daily activities. The results of the present review demonstrated that very few attempts to validate existing questionnaires have been made and that, when it has happened the quality of the evidence has been suboptimal (Table 4.2). The lack of comparative studies which aim to assess the validity, reproducibility and responsiveness of different questionnaires is striking and has contributed to uncertainties around the best measurement approaches in the TN field.

Chapter 3 highlighted the vast number of questionnaires being used in TN studies, with 10 and 9 different questionnaires used for pain relief and pain intensity, respectively. However, with the exception of the Penn-FPS-R, which demonstrated moderate evidence for content validity[517], the BPI-Facial demonstrated low evidence for inconsistent content validity and the TN QOLS has very low evidence for insufficient content validity. No data was available on the psychometric assessment for the majority of questionnaires identified in Chapter 3 for their use in TN studies.

Content validity is the most important measurement property and involving patients in development studies and validation studies is a requirement according to current guidance. [65] Confirming that the questionnaire is relevant, comprehensible and comprehensive from the patient perspective and for the context of use is at the core of a well-designed patient reported tool. The questionnaire should be able to capture the patient's experience of living with the disease and how it impacts on their lives. [529]

Regulatory agencies like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend the inclusion of patient reported outcomes and outcome measures on clinical trials. [530] This is particularly relevant for TN as most studies aim primarily to assess the effectiveness of treatment on pain reduction. In this context, a patient reported outcome should be used as a primary outcome/endpoint, given the inherent subjective nature of pain reports. In studies for which no objective primary outcomes exist the benefit of using methodologically sound patient reported instruments is even more critical.

The BNI-PS is without a doubt the most replicated outcome measure in surgical studies of TN, as seen in Chapter 3 Yet, no evidence could be found in the literature of any studies which aimed to validate the questionnaire to assess pain intensity in TN cohorts. Whilst is it recognised that the guidance available from COSMIN was not available when the BNI-PS was first developed, it has been widely available for at least a decade. Yet, the BNI-PS continues to be used and its scores perpetually compared between studies to draw conclusions on treatment effectiveness. This is probably due to its ease of use.

Similarly to the BNI-PS, the VAS has been extensively used in TN literature, with no evidence available for its content validity as illustrated in the present work. As outlined

in Chapter 3, the VAS has been used not only as a pain intensity outcome measure, as found in 85 of the 193 (44%) studies assessing pain intensity, but interestingly, in those assessing pain relief as well, as seen in 18 of the 314 (6%) studies assessing pain relief. [531] It is possible that it is also due to its ease of use although it might not be feasible for all patient populations.

The fact that there is a lack of evidence on the content validity of the two most widely used questionnaires for pain intensity and pain relief should be a concern to the field.

The BPI-Facial has demonstrated sufficient structural validity and internal consistency in a study of moderate quality. However, as explained above, it has failed to include patients in its design. As such, these positive results become meaningless in the absence of any evidence to demonstrate content validity. This questionnaire has subsequently been replaced by the Penn Facial Pain Scale Revised. [517]

Responsiveness was inadequately assessed for the TN QOLS and no studies assessed it for any other PROMs. Responsiveness is defined by COSMIN as "'the ability of an instrument to detect change over time in the construct to be measured". [532] When designing clinical studies of TN, where the expectation is that the construct under study improves to a certain extent, it is then important to utilise an instrument able to capture the change in scores from baseline to after intervention.

As discussed in the introduction, the importance of using validated questionnaires has been thoroughly described in the literature and the benefits of doing so highlighted. [69] Examples of this are the ability to compare study results and draw meaningful conclusions through meta-analysis. Another example relates to the waste of research resources when studies continue to be designed without incorporating psychometrically sound questionnaires. There is no doubt that this is essential for all

diseases, but it becomes even more so for rare conditions such as TN where financial support is scarce and recruitment of patients for trials can be challenging. [79, 533] Unusually for the pain field there are both medical and surgical treatments available for TN with the latter providing more long-term pain relief but with increased risk of complications. In such situations patients need to be able to compare these when making informed decisions about their treatment.

4.6.1 Limitations

Efforts were made to conduct an extensive search in five different databases with a validated search filter. However, the grey literature was not searched, which means that relevant studies might have been left out, which could have contributed to the evidence, helping to refute or support our findings. Additionally, authors of the appraised studies were not contacted for further clarifications due to time and resource constraints. Again, given the small number of studies and questionnaires eligible to appraise, obtaining additional information from authors could have added strength to the results.

Similar to what has already been described in Chapter 3 there are language limitations to be acknowledged as the search strategy was limited to studies in English. It is, therefore, possible that good quality psychometric studies published in other languages were excluded, which has biased the results obtained.

The limitations described above in relation to the methodology employed in this systematic review might help to explain why there were very few studies retrieved and why it has not been possible to make a strong recommendation for the use of any specific questionnaire.

4.6.2 Future directions

The results outlined in this review will be the basis for much needed future work to validate or develop questionnaires to be used in TN, more specifically to map those outcome domains of the core outcome set. However, at this stage we are unable to make recommendations for the use of any of the questionnaires included in this review, without further psychometric studies.

When designing a study to assess the measurement properties of an instrument it is important to have in mind the construct or domain of interest. [65] Working with TN patients will be crucial to clarify what outcome domains are important to them. It is hypothesised that domains other than pain will be of value to patients. For example, how much interference does the pain cause to their QOL, their daily activities or their mood? Results from a recent cross sectional study on the burden of illness support this hypothesis. [42] This information should, therefore, be taken into account in the design of future psychometric studies. Additionally, TN patients can present with different disease phenotypes, i.e., in some, the pain might be purely paroxysmal with variable periods of remission, but others might present with a continuous background pain, which persists in between the attacks. [534] Outcomes of surgical and pharmacological treatment appear to be worse in patients with concomitant pain. [22, 427, 535] These distinctive characteristics of TN should be taken into account when designing or validating questionnaires.

4.7 SUMMARY

The variability in the reporting outcomes, as described in Chapter 3, as well as the lack of validation of the instruments, as seen in this Chapter, highlights the need for a partnership between different stakeholders - patients, patient groups, clinicians, researchers - in the preparation of a well-defined core set of outcomes.

In Chapter 5, we begin the journey of working with the different stakeholders. Work conducted with Trigeminal Neuralgia patients to understand their lived experience and their preference of treatment outcomes is described.

CHAPTER 5 PATIENTS' PERSPECTIVES OF TRIGEMINAL NEURALGIA WITH EMPHASIS ON OUTCOMES OF TREATMENT – A QUALITATIVE STUDY

5.1 OVERVIEW

The involvement of patients in research has many advantages; patients provide information about how it is to live with a disease and exactly how treatment is affecting them, which can impact on the direction of research in the field. In this Chapter, a qualitative study conducted with patients with TN is reported on which gives rise to a comprehensive and complex description of their experience which goes beyond the hurt that pain causes.

Work arising from this Chapter has been accepted for publication in the Journal of Oral & Facial Pain and Headache. Sections of this Chapter have been taken directly from the manuscript.

5.2 KNOWLEDGE GAP

Few studies to date have explored – in depth – the experiences of patients from their own perspective utilising qualitative methods, nor examined the wider psychological and social impacts of TN.

Patients have seldom been involved in TN studies in a way that would allow the incorporation of constructs that are important to them in prospective clinical studies.[103]

Allsop and colleagues [111] conducted a qualitative study with focus groups involving 16 TN patients, identifying four main themes (diagnosis and support with TN, living in fear of TN pain, isolation and social withdrawal, and medication burden and looking for a cure). The study, however, did not aim to expand our understanding of what patients consider to be meaningful outcomes of treatment. These are essential in order to determine the best treatment approach from the patient's perspective. [536]

5.3 AIMS

The aim of the current study was to a) capture the description of the lived experience from the patient perspective and to b) highlight important treatment outcomes to inform an online Delphi survey with different stakeholders with the aim of developing a Trigeminal Neuralgia Core Outcome Set for clinical trials and other prospective studies (https://www.comet-initiative.org/studies/details/1123).

5.4 METHODS

This was a qualitative study incorporating online focus groups with TN patients. The reporting of the study follows guidance from the Standard for Reporting Qualitative Research (SRQR). [537]

5.4.1 Ethical considerations

This study received Ethical approval from the North of Scotland Research Ethics Committee (19/NS/0153). Those willing to participate were sent the study information leaflet and a consent form via email, which they completed, signed and returned,

before their allocated focus group. A copy of the consent form and the information leaflet is available in the Appendix 3.

5.4.2 Research team and reflexivity

The research team consisted of four researchers (three oral medicine clinicians and a health psychologist). One of the supervising researchers identified potential participants, and the other supervising researchers, who have extensive experience in qualitative study designs and focus group work, supervised the focus groups. The lead researcher was responsible for the recruitment of participants and running of the focus group and although also a clinician, introduced herself as a researcher, as the role of the facilitator might impact on the behaviour of the participants. [538] At the end of each focus group, a debrief meeting was conducted with emphasis on the facilitator's reflections and self-appraisal on their role as facilitator, researcher and clinician in order to minimise risk of bias[539]; feedback was provided to the group facilitator by two senior researchers. The analysis of the data was done independently by two researchers.

5.4.3 Participants and sampling strategy

The sampling strategy was purposive to include participants who had different TN phenotypes, i.e. different disease characteristics according to the International Classification of Orofacial Pain[10] – classic, idiopathic and secondary trigeminal neuralgia, with only paroxysmal pain or with concomitant continuous pain - along with participants who had been offered or who had received different treatments – medical and/or surgical treatments - and those who had experienced TN for a range of durations.

Participants older than 18 years, with a diagnosis of Trigeminal Neuralgia who attended NHS Facial Pain clinics in London and in Sheffield, from February to August 2020 were asked by their attending clinicians if they were willing to participate in the study. Participants needed to have a good command of the English language and be willing to participate in an online group discussion, to be considered for the study. There were no other inclusion or exclusion criteria. See Figure 5.1 for the flow chart of participants. Focus Group A&B run in August and Focus Group C run in September – there are no other differences in the two arms of Figure 5.1.

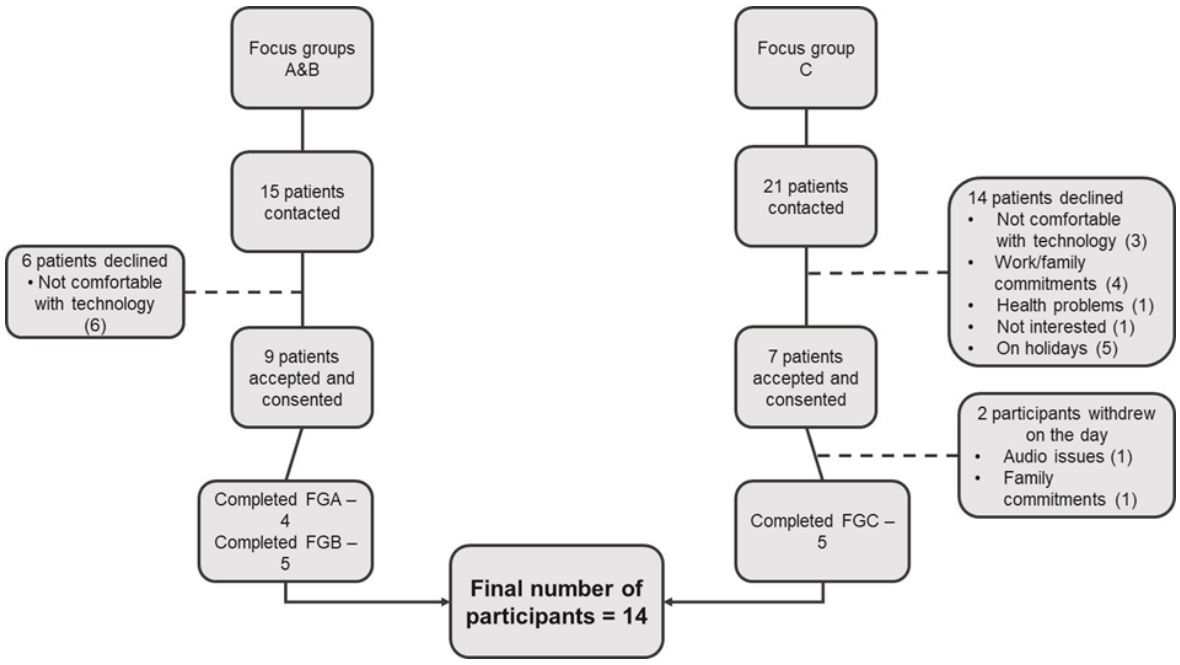

Figure 5.1 Flow chart of participant recruitment.

Thirty-six patients were contacted by telephone between August and September 2020. Three focus groups run using an online platform (Zoom Video Communications, Inc.) with a total number of 14 participants. Table 5.1 displays the demographic characteristics of the participants. Data is unavailable for those who withdrew on the day.

Table 5.1 Demographic characteristics of participants

Total number of participants	**14**
Gender	n (%)
Female	8 (57%)
Male	6 (43%)
Age (years)	Mean ±SD
Total	57.4 ±10.9
TN Classification	n (%)
Classic TN	7 (50%)
Idiopathic TN	7 (50%)
Secondary TN	0
Disease duration (years)	Mean ±SD
	7.6 ±4.8
Current management	n (%)
Medication	13 (93%)
In remission	1 (7%)
Previous surgery	n (%)
Any surgery	5 (36%)
MVD	4 (80%)
Radiofrequency	1 (10%)

SD= standard deviation; MVD= microvascular decompression

Due to the COVID-19 pandemic, the focus groups had to be conducted online. There are many advantages noted in the literature for conducting focus groups online rather than face-to-face. These include convenience for the participant to be able to join from their home, participation of a geographically diverse group, reduction of travelling and related expenses, all of which appear not to compromise the quality of the data obtained.[540] For face to face focus groups, some authors, like Krueger [541] recommend over recruiting to avoid running groups with a small number of participants due to last minute drop outs and to aim to have between 6-10 participants per group. However, as the online setting presents its own challenges, we aimed to recruit 4-5 participants per group. Some argue that the unit for analysis of focus group work should be the group itself and therefore, the total number of groups and not the total number of participants should be considered when talking about sample sizes.[542] [543] In this study, it was decided to stop recruitment once data saturation was achieved, instead of aiming for a minimum number of participants or focus groups. There are variations in the definition of data saturation but for the purposes of this project, it was defined as the moment at which the data collected had enough breadth and depth that it was adequate to answer our research questions. [544]

Focus groups discussions lasted between 70-90 minutes and participants were reimbursed a small fee for taking part.

5.4.4 Data collection

Focus group methodology was chosen to capture not only participants' experiences of living with TN but more importantly to allow group interactions and to allow participants to collectively explore and reach consensus as to what the outcomes of TN treatment should be. [545] [546] The main areas to be explored were (1) the lived experience of TN, for example, how participants would explain their condition to others and what the impact of TN was on different aspects of their lives, (2) what it meant for participants to live through a period where they had pain in contrast to ones in which they were pain free, (3) what participants understood to be a successful treatment and finally, (4) what treatment outcomes participants thought should be used in future TN studies.

A focus group open question guide was developed by the research team and checked for relevance and accuracy by a health psychologist, not part of the research team, with clinical experience in TN. The guide was based on the TN and chronic pain literature together with expertise from oral medicine colleagues. The focus group guide is included in Appendix 3. The questions were slightly edited following the first session based on feedback from participants, specifically relating to the question about their understanding of the condition.

Whilst following the question guide, the facilitator allowed conversations to flow between participants, only intervening either for clarification or to ensure that all the participants were given a chance to speak. [542] [545]

The focus group discussions were audio recorded and sent for professional transcription on the same day. The transcription was done *verbatim.*

5.4.5 Data analysis

Conceptual frameworks and thematic analysis of data

Trigeminal neuralgia, chronic pain and health related quality of life (HRQOL) literature such as the work conducted by Allsop and colleagues [111], Zakrzewska and colleagues [101], the biopsychosocial model approach of chronic pain treatment [547] and the Wilson and Cleary HRQOL model [548] were the lens through which the focus group data were analysed. The chronic pain biopsychosocial model and the Wilson and Cleary HRQOL models are well established and widely used in the chronic pain world. It was anticipated that themes like biological factors, such as pain intensity or side effects of treatment, psychological factors such as depression and anxiety, and finally social factors, such as social support and social interactions, would be identified within our data.

Although these conceptual frameworks were used to guide the process of identifying initial codes, an inductive approach to data analysis, where analysis was data driven, was privileged without attempting a rigid fit to the conceptual frameworks. [549]

Two researchers independently read and coded the transcripts multiple times and held several online meetings to discuss and refine the candidate themes and sub-themes. Data analysis was done manually using Microsoft Word (© Microsoft). For an example of the note taking and coding, see Appendix 3.

5.5 FINDINGS

Four themes and 14 sub-themes were interpreted from the analysis of the data of the three focus groups. Table 5.2 outlines the themes, sub-themes, and their descriptions. Each theme will be discussed, and key aspects described through the use of quotes from participants. The letters refer to the focus group and the number, to the participant. For a more detailed account of themes and sub-themes illustrated by participant's quotes, refer to Appendix 3.

Table 5.2 Description of identified themes and sub-themes

Themes	Sub-themes	Description
1. Characteristics of Trigeminal Neuralgia	1. Descriptors of TN	Participants' descriptions of the condition, using vivid vocabulary.
	2. Uncertainty about aetiology	Participants' account of having to deal with a condition for which the aetiology is not completely well understood and which has an uncertain prognosis.
	3. Prognosis – How chronic is chronic TN pain?	
2. Impact of living with Trigeminal Neuralgia	4. Psychological impact	Account of the many impacts TN has on mental, physical and social well-being – impact on activities such as working, eating, applying lipstick, kissing or hugging relatives – with emphasis on fear of triggering an attack.
	5. Functional impact and daily life activities	
	6. Social impact	
	7. Cognitive processes	Description of coping mechanisms developed by participants over time.
3. Navigating through treatment outcomes	8. The meaning of a successful treatment – *"I would like to get rid of it* (PAIN) *completely."*	Descriptions of expectations with regards to outcomes of treatment, with emphasis on pain levels, side effects of treatment, quality of life and mental well-being.
	9. Negotiating side effects	
	10. Supported self-management	Participant's descriptions of their willingness to self-manage if well supported.
	11. The intricacies of normality	Definition of what a "normal life" or "going back to normal" is.
4. Access, awareness, and peer support	12. Streamlined access to health care	Description of importance of early recognition of the disease by healthcare professionals which could speed early referrals to appropriate specialised care.
	13. Health care professionals' awareness	
	14. Peer support	Participant's account of the importance of the shared experience due to the invisibility of pain.

5.5.1 Theme 1 – Characteristics of Trigeminal Neuralgia

Most participants found it easy to describe the meaning and what prior knowledge they had about TN. All participants volunteered information on verbal descriptors of their pain but the majority expressed uncertainties about aetiology and prognosis of TN.

Descriptors of TN

Participants agreed that different individuals might experience TN differently. Some participants used pain descriptors like “stabbing”, “burning” and “exhaustive”. One participant used a more vivid description of their pain, comparing it to an angry hedgehog.

FGB1: “And I think as X said, it will affect different people in different ways, and depending how long you have been experiencing it, then obviously that may give you a whole different range of symptoms.”

FGC3: “Mine is a stabbing and then like a burning and then just exhaustion afterwards.”

FGC2: “I describe it more like a hedgehog just popping out from the side of my face, really angry and then throwing me down to the floor... A hedgehog inside my face.”

Uncertainty about aetiology

Most participants describe TN as a condition which happens without a clear explanation and which no one exerts control over. They describe that it is related to changes in the trigeminal nerve which are uncontrollable, and that the symptoms can happen randomly. Two participants went as far as describing that TN could be an issue related with the myelin sheath and one of them concluded that TN is random and uncontrollable.

FGA1: "It is a condition and it's something that just happens. I don't think anybody knows why it happens to some and not to others"

FGA2: "... as FGA1 said there is no explanation as to why it happens or whether there is a cure for it."

FGB2: "My understanding is that ... it is to do with the trigeminal nerve and I understand that the nerve is shooting and sends pain signals to different parts of your face … it could be to do with the myelin sheath wearing away and therefore coming in contact with something else..."

Prognosis - How chronic is chronic TN pain?

The uncertainty around the aetiology of TN was linked to similar uncertainties about the prognosis of TN. Most participants were preoccupied with the long-term behaviour of TN, its prognosis, and the longevity of the symptoms. They also worried about the lack of a curative treatment. Two participants used the words "fear" to express how they felt about the prognosis of TN.

FGA4: "… I was actually quite upset when I realised that I couldn't actually do anything about it and it's a long-term thing as well, it is not going to go away overnight."

FGB3: "I guess what comes to mind for me I guess is a fear to be honest, that it's progressive, that it typically or can get worse over time and so knowing how bad it has been or can be I guess an anxiety around it. If it is progressive, what does that mean?"

FGB1: "There is a degree of control which I can exert over it but there's always the fear factor that it's going to get worse, it's going to get more serious, and I am going to experience more of what other people experience having listened to stories from other sufferers."

5.5.2 Theme 2 – Impact of living with Trigeminal Neuralgia

All participants agreed that TN had a huge impact on different aspects of their life, psychological, social, or physically. For the majority of participants, eating was challenging in times of pain, and they avoided any possible pain triggers, such as brushing their hair or applying makeup or grooming. Participants displayed hypervigilant behaviour either in relation to their medication, what they could eat, or even about the weather (e.g., whether it would be windy or cold). This hypervigilant behaviour seemed to be associated with fear regarding uncertainty of the pain.

Psychological impact

All participants recognised the impact that pain had on their mood or emotional state.

FGA4: "I think it's quite an emotional thing anyway, this whole business (…)."

The word "fear", as mentioned above, was often used to express how they felt about the unpredictability of the disease and of a new attack. It was often associated with the construct of anxiety. Fear and anxiety were not exclusive to pain related episodes, but participants also reported them when they were pain free – on which all participants in the focus groups agreed,

FGB5: "(I agree) that fear and anxiety play a big part and not only when you're pain free but when you're experiencing pain and you're worried that it's going to get worse."

FGC5: "I think after a long period you are bound to get anxious and depressed because it is changing your life, it restricts your life... I think the difference with ours (pain) is that you cannot, it's unseen, people can't tell, you know."

I: "If you can think about a time when you were pain free and in remission, how would you describe this period? FGA3: "Still anxious sadly."

I: "Is there a consensus that there is a gratefulness and a relief when you are in a pain-free period but an underlying anxiety and worry? I: Almost a fear to do a thing that you think might trigger it. Would that be right?" "All: Yes, definitely."

The psychological constructs of catastrophising and hypervigilance were associated with episodes of pain but also with pain free episodes, prognosis of the disease, medication management and the side effects of treatment.

FGA1: "I never stopped carrying and taking my tablets (…) I have them in the car, I have them in every bag. I have got them absolutely everywhere in every pocket practically and I have little alarms to remind me to take them."

FGA3: "Like X was saying, everywhere around the house there's spare Primark glasses and pills so I know that they're there to hand. So while I enjoy it very much I do know that…well I don't know it's coming again I just assume it will come back and so, I think it's probably like being an alcoholic, you kind of think you're always aware that you can't do certain things because that will make it come back."

FGA1: "It's exhausting for you." FGA4: "It is, yeah. Because you're always thinking about it. There's not a moment where you're not thinking about a pain or the pain's there, oh what is it today, what is it going to be. You've got to take your tablets obviously throughout the day and that reminds you that you've got to take them because you've got the pain and it just invades all your life really."

Functional impact and daily life activities

The impact on activities of daily living, although mostly associated with eating due to the possibility of triggering pain, also had an emotional impact as participants tended to avoid close and intimate contacts. They needed to be alert to their surroundings

and avoid, for example, cold or breezy weather as they felt that this may trigger a pain episode.

FGC1: "I actually have to be careful how I eat. So if I eat a sandwich, for instance and I press down too hard on my lip then that is totally excruciating so when I'm actually out eating I have to be careful how I eat, how I drink as well. (…) obviously going outside the cold and the wind I have to be careful where I go, especially in winter but for me."

FGC4: "Yeah, I'd like to say I completely agree. I find before I go out now I have to check the weather and see if it's going to be cold or raining and things like that."

FGC3: "I've not being able to eat solids for over two years, I had to blend all my food so I'm always really anxious people are going to say oh, shall we go for a bite to eat or something like that and then I have to explain why I can't."

FGA3: "Lipstick is not something that you'd put on. Or I think one of the saddest things I think was just kissing someone." FGA2: "Oh that is the worst!" FGA3: "Or hugging someone."

Social impact

The social impact of pain was linked with work, social interactions and participation in social activities, such as dinner parties. Pain in some instances threatened social participation, as participants tended to display avoidance behaviours as self-protection mechanisms in fear of triggering a painful attack. One participant described this behaviour as "withdrawal".

FGB4: "I think the word I'd use to describe where I was at is withdrawal. No semblance of normality, you're very conscious of the potential of what could go on around you and it's almost like playing a game of statues, you just want to minimise any possible interaction that could cause you kind of movement in your face, talking, eating, whatever it happens to be and I'm under no illusion it makes it very difficult for someone who is living with you just because you become more and more withdrawn."

A few participants described that TN impacted on their work, not only due to the difficulties in talking and communicating effectively with others but also because they felt the need to hide their disability from others.

FGA4: "I only work part time, I work with small children at a preschool so I just push through and try to avoid things if I can. If I can't speak, I try to avoid talking to people and just keep out of the way.

FGA3: "So I have had TN for eight years and I did have to take time off work because ... my job involves talking to a lot of people... you kind of start talking and then you think you can't say what you are diagnosing... you look like you don't know your job."

FGB1: "From a professional capacity (…) sometimes the symptoms caused difficulties talking. I can work from home so that sometimes reduces the almost embarrassment (…) because it is not something you actually want to be broadcasting to your colleagues because it becomes a bit debilitating, and you want to keep that from them as long as you can."

It was striking that participants described feeling isolated as no one could see their pain due to an absence of visible symptoms/signs. The lack of social validation and the seeming lack of knowledge as to how much disability TN could cause resulted in many participants reporting a sense of isolation.

FGA4: "My work colleagues know that I have got something wrong, but they don't fully understand what it is, and I think that is the thing, a lot of people don't actually understand what it involves and how it affects you because you look normal, we all look as if there is nothing wrong with us... so there's nothing obvious on the outside but they just don't realise the pain and how it invades yourself when you have it. So, I find that difficult sometimes."

FGC1: "A lot of people think there is nothing wrong with you because they can't actually see anything at all but they don't realise how much pain you can be in."

FGC2: "It does not seem that common (TN) and so therefore, other people don't have any understanding of it (…) so when it does strike you can feel a little isolated with it…)."

Cognitive processes

Although most participants described changing their behaviour to avoid situations where their pain could be triggered, they nevertheless also reported developed coping and adaptive strategies, either through reading, with the help of healthcare professionals, and a few, on their own, for example, through mindfulness.

FGA3: "I think initially I used to think well people used to say well you just need to calm down and I used to think [laughs] I don't really know that I'm not calmed down and then obviously the more that you read about it or when you actually know that's what you've got it's easier to accept it and understand that it's not something that you're doing, it just happens and the best way then it just to move forward with it."

FGB2: "I think I am in a good place at the moment, but without the support of the clinic, I would feel panic".

FGA2:" But I think I've reached the point where I can accept it's there and I don't want to take any more medication but if it then starts getting worse then I will increase it."

FGB1: "Mindfulness actually helped me control the pain. It didn't make it go away but it helped to control the pain and put me back in control."

Some participants compared TN to other conditions; this shift in their conceptualisation of the disease appeared to allow for improved coping mechanisms.

FGA4: "When Covid all kicked off and you're seeing all these poor people being put into intensive care I just thought as long as I've got my oxcarbazepine I can cope with anything."

FGA2: "I think sometimes though, if you thought you had heart disease or diabetes you wouldn't think twice about having to take medication to prolong your life or make you feel better (…) so if it makes you feel better (the medication) it's better to increase it (…) so that you tip over the edge of being in constant pain."

5.5.3 Theme 3 – Navigating through treatment outcomes

The meaning of a successful treatment – "I would like to get rid of it (PAIN) completely."

All participants were very clear about their expectations with regards to treatments offered; they wanted to be 100% pain free. Nevertheless, most were willing to compromise having side effects in favour of pain relief.

FGC1: "I would have sold my soul to the devil just to change that" (the levels of pain regardless of side effects).

Others would accept having the pain as long as it was less intense and the attacks were less frequent.

FGA2: "Yeah, I would say ideally success would be pain free, off the medication."

FGB4: "I think it is a sliding scale actually because anyone who has been lucky enough to get remission from either medication or indeed surgery, the bar is pretty high, so you start saying well, the first thing I'd really expect or like is to get absolute total remission for good."

FGA3: "I think the severity of the pain. If it wasn't so severe. If I had to have it all the time but it was just dull I would rather that than the sharpness of it. So probably just to reduce the intensity of it."

FGC4: "Yeah, I would like to have something that would just take it away completely – definitely. Those little niggly pains and jumping to big pains and all of that – I'd like to get rid of it completely."

FGA4: "Yeah, I think the intensity as well. I can live with it if it's just there. I can live with that but when it gets to be really intense that's the thing for me, definitely. It's just getting rid of that intensity of pain, definitely... Like if you have this constant dull ache and it just stays there that's fine, it's when you have the dull ache and then it's going [makes shooting noises]. FGA1: Yeah, that's the worst thing. Yes, the shootingness that just catches you. Once you've got that under control you kind of think oh, actually I'm so much better than I was."

Negotiating side effects

A few participants worried about side effects of surgery, specifically numbness, and would not consider surgery because of this - unless it was their last option. Most participants had experienced medication side effects, specifically related to weight gain, feeling slower, drowsy, and forgetful. On balance, most participants appeared to accept some side effects providing their pain was well controlled.

FGB2: "I would say it would be nice not to have the side effects, but if you balance that against the pain, I would rather have the side effects than the pain."

FGB3: "I would agree with that entirely. I find myself now and again, (…) searching for the right word. Definitely tired. (…) It could be controlled for me and absolutely I would take the side effects in a heartbeat over the condition."

FGA3: "I just think the fear of numbness as well, with the surgery I don't know if I'll be able to live with being numb rather than in pain. I'd rather have this dull ache than have a numb face I think."

I:" So, if you had to choose the outcomes of treatment, would these be pain relief, intensity, looking at the quality of life you have living with TN and the side effects of medication?" All in FGC: "Yes!"

Supported self-management

Most participants agreed that having support with their mood and with coping strategies would be beneficial, specifically as their coping mechanisms could be influenced by different stages of their journey, whether they were in remission or not. For example:

FGB5: "Ideally pain free either with the drugs or into remission (…) – that would be fantastic. But I also think on top of medication it's being able to have support through talking therapies and when I was in a really bad state, I did talk to a clinical nurse specialist and that really helped… although she couldn't take away the pain it just helped me. So I'd come off the phone feeling right, I can do this, I can do this so it was really helpful. I wouldn't take her away, she's a really important part of it."

FGA1: "So I think ideally complete pain relief but if not then at a level that I feel that I could cope with it."

FGA2:" For me it depends on what particular point you are at. If you are in a period of remission you just want it to carry on and you'd like a magic pill for it never to happen again (…) when you are in the darkest days I could find myself saying, if this could reduce to this particular levels I could accept it."

FGB5: "I would agree that fear and anxiety play a big part and not only when you are pain free but also when you are experiencing pain and you are worried that is going to get worse. So in terms of treatment, I would say that for me, it would be really nice to be able to talk to somebody, a professional really regularly to just talk through things. I think that's really important because sometimes you do feel on your own. (…) maybe a psychologist or somebody you can just talk things through with and I think the very action of actually talking about it would really help."

The intricacies of normality

Finally, some participants gave an account of what normal or almost normal life would look like to them:

FGA2: "So about six months ago I was absolutely just pain free, no symptoms, back to normal."

FGB5: "So it's never quite back to normal because I've got that in the back of my mind, little things that I know might be triggers, even though I'm having a period

when I haven't got the pain I'm just very, very careful eating different things and stuff just to keep it off, keep it away just in case."

FGA4: "I think it's being pain free definitely, that's the main thing because that's the main thing that affects everything isn't it really, is having that pain and if you haven't got the pain obviously you can just carry on your life as normal. So I think the pain side of it is for me the most important, definitely."

5.5.4 Theme 4 – Health care access, awareness, and peer support

Streamlined access to health care

All participants agreed that having streamlined access to health care support is extremely important. One participant compared losing the support of her consultant to losing her own mother.

FGA3: "So even when I saw her in March she sort of said do you think you still need me? And it's like losing your mother, it's like oh God, yes do not suggest that I don't come anymore because I know I don't have it right now but I really don't want to be back there to the point of having to go to see her more regularly."

FGC4: "I would like to have someone at the end of the phone I could speak to, if I have got any problems. I have spoken to the clinical nurse a few times and she helped me with medication. (…) So it is always nice to have someone there just so they can understand what you are going through and just to help you out with things."

FGA3: "I felt it was really through Dr Y, she said try to get more sleep, try to exercise a bit, try to get that balance right which luckily with my husband we arranged that or sorted it so that I didn't work full days for a while and did that sort of thing. So, since last October through going to see Dr Y, I've reduced my medication and at this moment I'm not taking any. So while you all, like X said, look forward to a life of constant medication there is I think a light."

Health care professional's awareness of TN

Most participants agreed that healthcare professionals, mainly GPs and dentists should be aware of TN, not only to support patients through their journey but to avoid delay in care or unnecessary treatments.

FGB4: "X had a really good experience with a GP but generally, GPs don't understand that it's such a rare condition they don't understand what it is and they don't understand that your medication can change, that you can be on something and then you need to reduce it and then you need to come up again or you need to change to a different drug."

FGA4: "I think it's upsetting that the dentists don't realise that TN could be the reason for your pain. Why don't the dentists know in the first place to explore that option? Because I thought mine was dental as well, to start off with (…) why don't the dentists consider that as an option before they start taking nerves out and

messing about with your teeth? I find that really upsetting and annoying because I think the dentists should be more aware, at the end of the day."

FGC3:" It took so long to get diagnosed that it just adds to the misery of it."

Peer support

Participants also felt that talking to others with the same disease could be helpful and offer hope.

FGA4: "I think it's nice just to speak to other people. I've never actually spoken to anyone else that has got this apart from the people that I'm speaking to today. Just to speak to people and you know, like X said, today she is pain free and she has been for a while, I think just that reassurance that it can happen and obviously you know that yourself. But then I think just to speak to other people and to get an understanding from other people from the things that they've been through I think is really helpful. And everyone has that fear and you have to deal with the fear. It's really nice to speak to other people."

5.5.5 Summary of findings

Figure 5.2 illustrates the intricate relationship between the four themes and 14 sub-themes interpreted from the data, which will be elaborated on in the discussion.

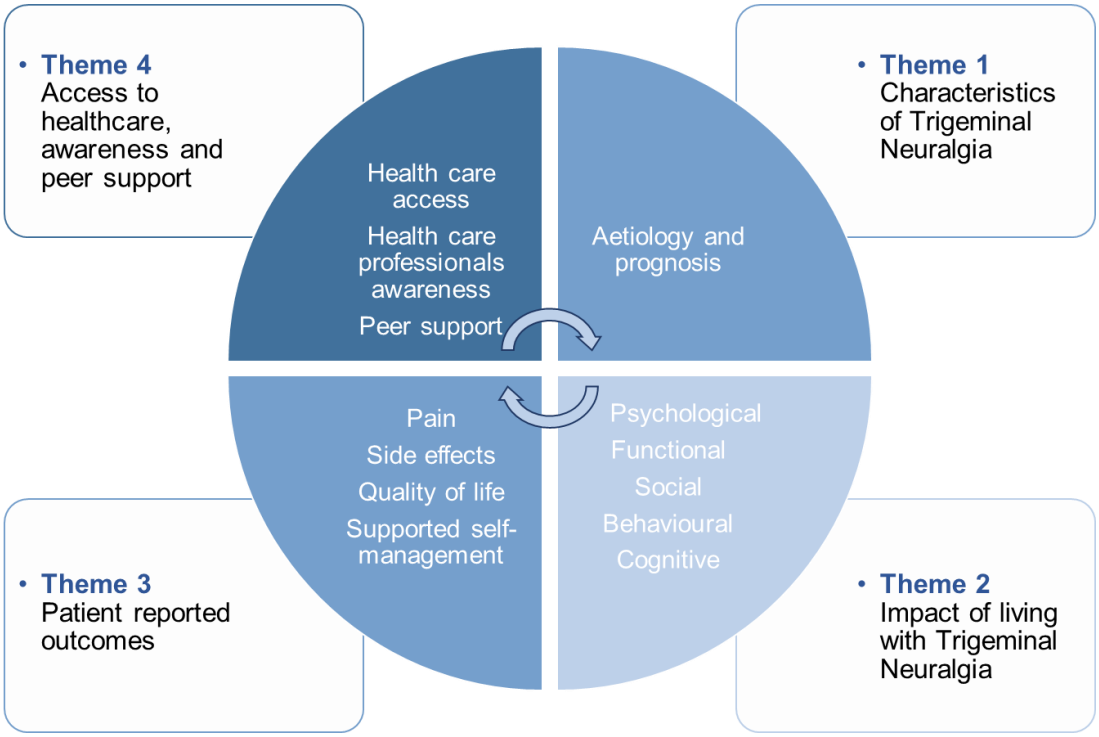

Figure 5.2 Interconnectedness of themes and sub-themes

5.6 DISCUSSION

This is the first qualitative study exploring TN patients' preferences regarding outcomes of treatment. Participants clearly defined pain reduction as the most important treatment outcome, although improving QOL and having supported self-management were also seen as important. The findings from this study provide a comprehensive and detailed account of the meaning of living with TN from the patient's perspective. This is really important as, like so many other chronic pain conditions[550-552], TN impacts on different aspects of daily living and it is important that we understand these different impacts from the perspective of the patient themselves.

It is important to note that, although the four themes and 14 sub themes were constructed from analysing the data, these should not be interpreted individually. This is because they are all, to some extent, interconnected (see Figure 5.2). The pain attacks' unpredictable nature and the long-term prognosis of the condition (Theme 1) have an impact on the participants' mood (Theme 2). Due to TN's pain unpredictably (Theme 1), participants often avoid attending social events in fear of an attack (Theme 2), which in turn causes upset (Theme 2). The sub themes included in Theme 2 are strongly inter-related. The participants' account of their actions in social circumstances, whereby they actively change their behaviour to avoid triggering pain, by avoiding eating in public or by not kissing or hugging others, is indicative of a coping strategy albeit perhaps a maladaptive one, due to the negative impact on their emotions. Positive examples contrast with the latter, whereby participants have tried to develop ways of managing their pain experience by using alternative treatments, reading and improving their knowledge of the condition (Theme 1) or even trying to manage their medication intake to minimise the intensity of their pain (Theme 3). Similarly, participants' reappraisal of their long-term condition in comparison to other

chronic conditions (Theme 2) allows for a reconceptualization of TN and improved coping mechanisms.

Unsurprisingly, the conceptual frameworks used as our initial guide provided accurate constructs, helping make sense of our data. The biological pain related constructs such as pain characteristics, feature in the biopsychosocial model of chronic pain [547] and in the Wilson and Clearly HRQOL model. [548] These are not static models, and these constructs have a dynamic relationship with subsequent ones, as the level of pain might influence one's ability to eat or the unpredictability of the disease can influence someone's fear of an attack which in turn can cause behavioural changes. The qualitative work by Allsop and colleagues showed the importance of fear in the journey of participants living with TN. [111] Similar to the experiences described in their work, participants in our study used the word "fear" very often and linked it with many constructs, such as prognosis (Theme 1), anxiety and behavioural changes (Theme 2), the side effects of treatment (Theme 3) and in peer/healthcare support (Theme 4). The risk of pain related disability caused by avoidance behaviours is well known in the field of pain psychology. [103] Participants' descriptions of how their behaviour needs adjusting due to fear of pain are consistent with the Fear Avoidance Model (FAM) [553].The model illustrates how through learning, behaviours change to prevent pain related stimuli. The behaviour is then maintained, and it is argued that it contributes not only to the maintenance of pain-related fear [553] but also to increased pain. [554] There is a dynamic and possibly reciprocal association between constructs, although this reciprocal relationship is yet to be confirmed in TN patients.

Participants' descriptions can also be interpreted using Leventhal's common-sense model of self-regulation. [555] This is another dynamic framework for understanding how emotions patients experience when faced with a threat to their health can influence their cognitive process or perceptions. . For example, the unpredictable characteristics of TN (Theme 1) – cognitive illness representation - can impact on emotional well-being (Theme 2) - emotional illness representation. Cognitive and emotional illness representation drive cognitive processes of coping (Theme 2). Healthcare systems and communication about health and disease can influence illness representation. [555] In this group, participants did emphasise the importance of an accurate and timely diagnosis and of support from health care providers (Theme 4). Although not modifiable through treatment, changes to the way information is transmitted to patients and the improved accessibility to services is likely to contribute to the patient's journey, decreasing the emotional distress caused by uncertainty of diagnosis and prognosis (Themes 1, 2 and 4). Participant's descriptions have highlighted their ability to shift their response to disease and its management (Sub-theme 7).This is better explained by the theoretical model of Response Shift which describes a shift in response to a person's appraisal of a construct, for example, perceived QOL, either by a change in internal standards, values or conceptualisation; the change would be driven by behavioural, cognitive or affective mechanisms influenced by the person's antecedents which can impact on how they appraise the construct under study. [556] This model has recently been revised to allow a distinction between the construct and the measurement of the construct by using a patient reported outcome (PRO), for example, as well as to allow response shift to be investigated at different time points. [557] This is important for TN patients as their understanding of different constructs will

likely change depending on if they are in pain or pain free and should be taken into consideration when analysing PRO data.

When asked specifically about what outcomes they wished to have following treatment, participants clearly agreed on complete pain relief or reduction in pain intensity as the primary goal of treatment, but they also agreed that side effects and improving quality of life were relevant. These findings are not surprising, and a recent European survey of 487 chronic pain patients identified that their main goals were pain reduction (91.2%), taking part in family and social activities (72.5%) and household tasks (68.1%).[558] Although reducing pain is of utmost importance, as demonstrated by how participants drew a parallel between “normal life” and a “life without pain or pain free” (Sub-theme 11) having support to engage in self-management, either with the emotional impact of TN or with their coping mechanisms, is important (Sub-theme 10) and, as discussed above, constructs such as anxiety, fear, avoidance and coping arose from the participant’s descriptions of their journeys.

As described in the data collection subsection, focus group methodology was chosen to allow interactions between participants. Additionally, focus groups allow participants to compare their experiences which contributes to the richness of data. In comparison with one-to-one interviews, focus group data are not as in depth and detailed but are very rich and include different perspectives, hence why focus group work was privileged in the present study.

Due to the COVID restrictions the focus group work was conducted online. One-to-one interviews are often chosen when the subject under enquiry is sensitive but online focus groups appear to give patients confidence to share more sensitive content. Although the questions were not aimed at sensitive topics, during data collection

participants seemed to be at ease when sharing the more negative impact of TN on their personal lives. One of the explanations for this might be the fact that participants were in a comfortable environment of their choice.

The online setting poses challenges such as the inability to pick up non-verbal cues and engaging participants might not be as easy as in a face-to-face setting, which might influence the data, however, recent evidence in qualitative research in the rare disease context suggests that qualitative data collected using online versus face-to-face focus groups are very similar in terms of number of transcripts generated, number of codes generated and similarity in code presence. [559]

5.6.1 Limitations

The sampling strategy was purposive, and patients recruited according to the most up to date TN classification. Although this allows for rigorous and more stratified recruitment of patients, which can facilitate future comparisons with studies using the same classification, one might exclude patients who have TN, but who have been labelled using different classifications.

An attempt has been made to recruit patients with secondary TN but this was not achieved in this study their preferences have not been identified. Although it is anticipated that their TN pain experience is similar, these patients have generally worse outcomes when compared with patients with other types of TN due to their comorbidities and polypharmacy.

The focus group question guide was reviewed by a health psychologist prior to the start of the data collection but it was not piloted by TN patients neither by a patient nor a public involvement expert panel (PPIE). This might explain why the question guide had to be slightly edited following the first focus group. Specifically, the question about the patient's understanding of their condition had to be modified.

The researcher facilitating the focus group work and analysing the data was a clinician with prior clinical experience in TN. Although steps were taken to ensure that the data collection was not influenced by the facilitator background, as described in the data collection subsection (5.4.4) it is important to acknowledge that their background clinical knowledge as well as their prior knowledge of the conceptual frameworks could have influenced data analysis, and therefore biased the results.

5.7 SUMMARY

Data presented in this Chapter have important implications for the field of TN. For the first time, patient's views were considered, and outcomes that matter to patients have been identified. Through their direct accounts, and by analysing and interpreting the data, it was possible to appreciate the intricacies and complexity of living with a chronic and unpredictable painful condition. In the next Chapter, and building on from this and Chapter 3, the final steps to develop the COS for TN are described.

CHAPTER 6 CORE OUTCOMES IN TRIGEMINAL NEURALGIA – A MULTISTAKEHOLDER PERSPECTIVE

6.1 OVERVIEW

Having identified the most commonly used outcomes in the published literature and having asked patients to contribute their lived experience knowledge as well as their preferences as to what outcomes are important, this Chapter will describe the integration of that information which was included in consensus processes that led to the development of a core outcome set.

Work arising from this Chapter has been published in The European Journal of Pain (open access, 2022) and the complete reference is in Appendix 5. Sections of this Chapter have been taken directly from the manuscript.

6.2 KNOWLEDGE GAP

TN is a unique type of facial pain for which pharmacological and surgical options are available. [2] The first line treatment is the anticonvulsants carbamazepine and oxcarbazepine; other adjuvant options are available when these are not effective(gabapentin, pregabalin, lamotrigine and baclofen) but this recommendation is based on weak evidence only. [6] When medication alone is either not effective or it causes intolerable side effects, a surgical option must be considered. The treatment of choice for those who have neurovascular compression and are fit enough for posterior fossa surgery is microvascular decompression. For the remaining patients, ablative techniques can be used. [6] Despite these options, no consensus exists yet as to what is the optimal treatment. The lack of randomised controlled trials, comparing

the different drugs[83], drugs and surgery and the different surgical procedures, partly explains the lack of a clear choice when it comes to treatment. Additionally, the lack of standardised outcomes and outcome measures used contributes to the heterogeneity of data and the growing inability to compare study results. The need for more standardised outcomes and for the assessment of end points other than those related to alleviation of TN pain has been highlighted over the years in relevant disciplines, e.g. neurology guidelines. [5, 560] In the wider chronic pain field, the IMMPACT group (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) has provided general recommendations on what outcomes should be measured in chronic pain clinical trials and these include four outcome domains besides pain, for example, the emotional and physical impact of the condition, satisfaction with treatment and adverse events. [86]

The lack of information on outcomes fails to provide patients with adequate answers about the prognosis of the treatment options available, and just adds to the waste of research results. These research challenges could be improved if the wider research community assessed the same outcomes in a standardised way.

A core outcome set (COS) is defined by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative as “an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care”. [43] In addition, the outcome assessment should also be standardised, and in the case of TN, through valid, reliable and responsive patient reported outcomes (PROMS), due to the subjective nature of pain and other constructs, such as quality of life.

6.3 AIM

The aim of this study was to develop the COS to be used in all future TN clinical trials (medical or surgical).

6.4 METHODS

6.4.1 Study overview

The TRINCOS study was designed to develop the core outcome set to be used in clinical trials (medical or surgical) of adult patients with TN, as defined by the International Classification of Orofacial Pain. Methodological guidance was sought from the COMET Initiative. [43]

The reporting of this study followed guidance from the Core Outcome Set–STAndards for Reporting COS-STAR Statement. [125] A registry entry was prospectively created for this study on the COMET Initiative website - https://www.comet-initiative.org/Studies/Details/1123.

6.4.2 Study design

Consensus methods were used to achieve the present study's aim. The Delphi method was developed by RAND Corporation in the 1950s. It is a structured communication method of obtaining consensus on a given subject by a group of experts. [561] It has specific features which distinguish it from a traditional survey, for example, it must have at least two rounds to allow for feedback between rounds[43], there is an assessment of the responses, participants can modify their responses between rounds, and it is an anonymous process.

The advantage of this survey is that responses are more independent and not influenced by participants' status or perceived knowledge or expertise. [561]

A consensus meeting is a process by which a group of people, usually experts on a given subject, meet face to face (or online) to debate, discuss and generate agreement on a given issue. By the end of the meeting, the group should reach a consensus, which differs from unanimity. Not all participants are unanimous in terms of the preferences, but there is a shared agreement by all. There is no specific guidance on how to run these meetings for a COS development study. In view of the recent need to shift to online meetings, guidance was sought from COMET on how to best prepare for the format change. [138]

6.4.3 Participants

Delphi survey

The sample size for a Delphi survey does not rely on statistical power, as opposed to a traditional survey, where it is expected that the results are generalizable to a larger population; nevertheless, the recommended panel size is between 10-18 participants. [561] The focus of recruiting for a Delphi survey is on the expertise of the participants in a given field. [562] The results of the Delphi will depend on the ability of its participants to provide input based on their background knowledge. [563] In the case of TN, clinicians, researchers, and patients were the stakeholder groups identified with the right expertise to contribute to the consensus processes. Patients were recruited from a patient organisation, the TNA UK (Trigeminal Neuralgia Association). The study was advertised on the TNA website and newsletter. Patients contacted the study team if

they wished to be included in the study. European and international patient association representatives were contacted via the email addresses available on their webpage.

Healthcare professionals and researchers, including industry representatives, were initially selected via http://expertscape.com, a website that features the researchers with the greatest output in a given area, and later contacted via email. Some of these researchers are also healthcare professionals. Those contacted were asked to forward the survey link to colleagues and contacts (snowball sampling). Healthcare professionals known to the research team were contacted directly. The members of the research team did not participate in the survey.

Email invitations with details of the study, contact details of the research team, and the survey link were sent to prospective participants. A copy of the email sent to professionals and to patients as well as the information leaflet are included in Appendix 4.

Online consensus meeting

Healthcare professionals and researchers who completed the three rounds of the Delphi were randomly selected and invited to participate. To increase generalizability of results, a new cohort of patients was recruited from a Facial Pain clinic at London Teaching Hospital.

The aim was to recruit between 15-18 participants to allow for small group discussion, with a balanced number of participants per stakeholder group. Those attending received a voucher for their time and contribution.

6.4.4 Information Sources

The content design of the Delphi survey was informed by the qualitative focus group study conducted with TN patients (Chapter 5). It was also based on the results of the systematic review summarising the outcomes and outcome measures used to date in TN intervention studies (Chapter 3). For completeness ClinicalTrials.gov website was consulted for information on outcomes planned in newly registered trials.

The final list of outcomes was reviewed by the research team and outcomes were combined using the IMMPACT taxonomy for clinical trials in chronic pain as a guide[86] but domains were not restricted to those recommended in the guidance and others were included.

Prior to the start of the Delphi, the survey questionnaire was piloted with three patients and three clinicians and feedback was sought on clarity of the questions and terminology, definitions of the outcomes and time taken to complete the survey. Their suggestions were considered before the survey was finalised. The final list of domains and outcomes is in Appendix 4.

6.4.5 Consensus processes

Delphi survey

Patients, clinicians and researchers were invited to participate in a 3-round Delphi survey. Each round was open for four weeks. The Delphi Manager software developed by the COMET Initiative was used to set up and run the online survey. [137]

In round 1 the outcomes were listed in random order. Participants were asked to score each outcome to reflect ‘how important’ they felt they were on a Likert Scale from 1-9,

with 1- 3 labelled ‘not important’, 4-6 labelled ‘important but not critical’ and 7-9 labelled ‘critical’. If they could not score an item, an option “unable to rate” was available. At the end of Round 1, participants were able to suggest additional outcomes that they thought should be considered but had not been featured in the survey. Those who did not complete Round 1 were not invited for the next round. In Round 2, the distribution of scores awarded for each outcome during round 1 was summarised and divided by stakeholder group. The summary of scores per stakeholder group was visible to participants and they were asked to re-score each outcome for importance considering their own group scores. This method has been shown to increase consensus. [564]

Similarly to round 1, only those completing Round 2 were invited for the next round. In Round 3 the distribution of scores was summarised and sent to participants. They were again asked to re-score the outcomes as described above. By repeating the process in three rounds, using group score feedback, can encourage convergence of ideas. No outcomes were excluded (either having reached cut off for inclusion in or exclusion from the COS) to give each outcome an equal change of highest level of consensus. [565] Although summaries of scores were visible to participants, anonymity of participants personal details was maintained throughout the process.

The criteria for determining which outcomes should be included (consensus in) and which should be excluded (consensus out) were specified *a priori*. An outcome was considered “in” if 70% or more scored it as a 7-9 and fewer than 15% scored it as 1-3, in all stakeholder groups. An outcome was considered “out” if 50% or less scored it 7-9 in all stakeholder groups. [566] Outcomes for which a consensus was not reached (no consensus), were taken forward for further discussion at the online consensus meeting.

Statistical analyses

Descriptive statistics were used to summarise the data set (number and percentage of those scoring each outcome, by stakeholder group). Overall attrition rate was calculated and mean scores of those completing round 1 alone were compared to those completing round 1 and 2, and mean scores of those completing round 1 and 2 only, where compared to those completing the 3 rounds. A t-test was used to assess if the differences in means were statistically significant ($p<0.05$).

Online consensus meeting

A meeting package was designed with the help of a patient who did not take part in the consensus process and sent via email to those who accepted to participate. Guidance was sought from the COMET website for plain language summaries and their video explaining what a COS consist of was sent along with all the meeting package documents (consent form, glossary of terms, a list of outcomes which had reached consensus at the Delphi, the list of outcomes to be discussed at the meeting, the meeting agenda). This information is available in Appendix 4.

A 3-hour online consensus meeting was held using an online platform (Zoom Video Communications, Inc.). The aim of this meeting was to discuss the outcomes which did not reach consensus during the Delphi survey followed by a new anonymous vote using the same criteria as that of the Delphi survey and, to hold a final majority vote (i.e., >50%) if the provisional COS included an extensive list of outcomes. Although there is no clear guidance on what an ideal number of outcomes should be in a COS, based on the OMERACT guidance [567], the aim was to generate a list of approximately 10 outcomes for the ease of implementation and feasibility.

6.4.6 Ethical approval

A consent statement featured in the registration page of the Delphi survey, and only those who consented to participate could progress through the survey pages. Ethical approval for the consensus meeting was granted by North of Scotland Research Ethics Committee (19/NS/0153). A copy of the consent form for those participating in the consensus meeting can be seen in Appendix 4.

6.5 RESULTS

6.5.1 Delphi

Figure 6.1 summarises the flow of participants through the Delphi survey. Demographic and clinical data were collected at the start of the survey and participant rates are in Table 6.1.

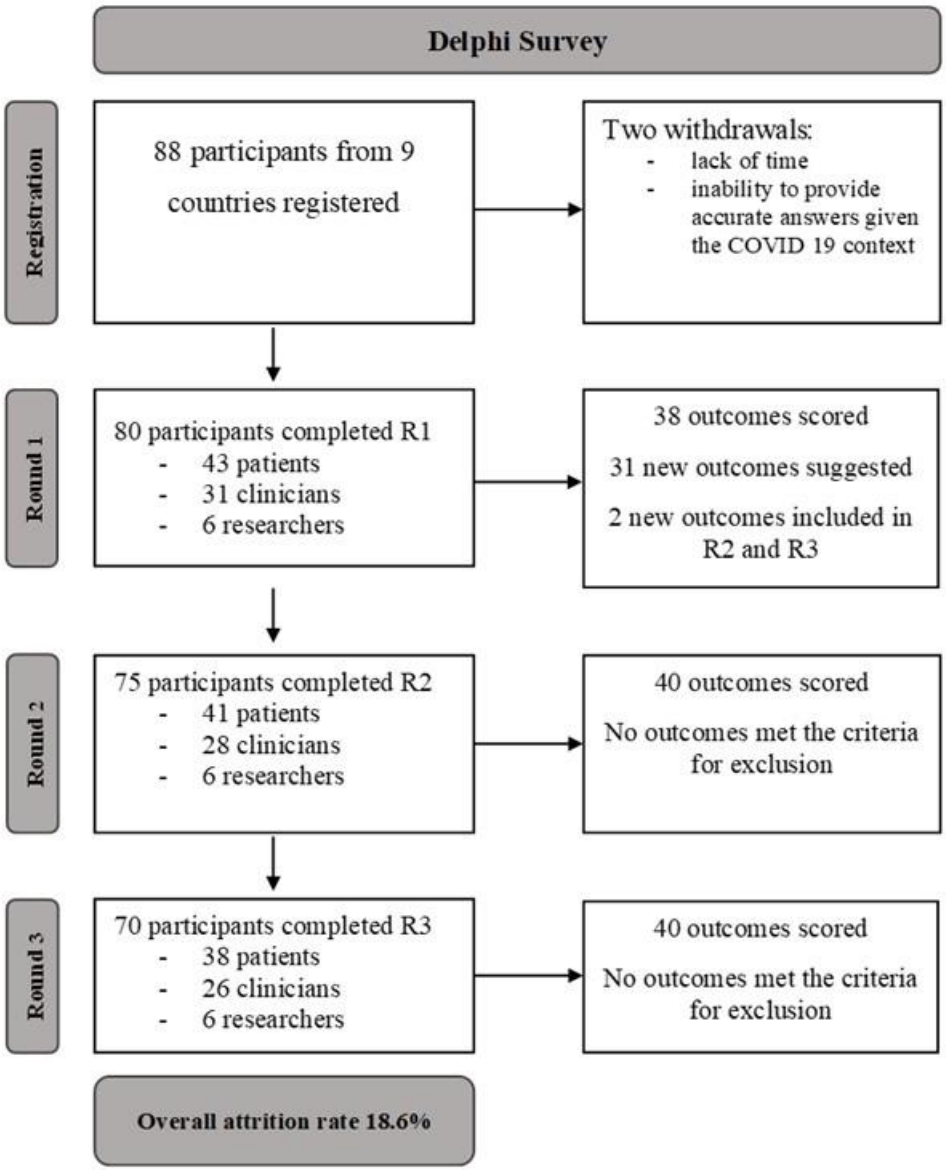

Figure 6.1 Flow chart of the Delphi survey.

Table 6.1 Demographic data of Delphi survey participants

	Delphi Survey					
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
Patients/patient's representatives						
Registered	47	100.0	43	100.0	41	100.0
Completed	43	91.5	41	95.3	38	92.7
Females	25	58.1	23	56.1	20	52.6
Age, years						
<45	7	16.3	6	14.6	6	15.8
45-65	18	41.9	17	41.5	14	36.8
>65	18	41.9	18	43.9	18	47.4
Country of residence						
United Kingdom	39	90.7	37	90.2	34	89.5
Germany	1	2.3	1	2.4	1	2.6
Canada	1	2.3	1	2.4	1	2.6
Denmark	2	4.7	2	4.9	2	5.3
TN diagnosis						
less than 2 years ago	12	27.9	10	24.4	9	23.7
2-5 years ago	7	16.3	7	17.1	5	13.2

Delphi Survey						
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
> 5 years ago	23	53.5	23	56.1	23	60.5
Not applicable	1	2.3	1	2.4	1	2.6
Type of pain experienced						
Acute attacks and I always have a background pain (burning; aching)	9	20.9	9	22.0	9	23.7
Acute attacks but I am pain free in between attacks	21	48.8	20	48.8	19	50.0
I am in remission (pain free)	10	23.3	9	22.0	8	21.1
Not applicable	3	7.0	3	7.3	2	5.3
Treatments to date						
Medication only	25	58.1	23	56.1	22	57.9
Medication and surgery	16	37.2	16	39.0	15	39.5
Alternative therapies only	1	2.3	1	2.4	0	0.0
Not applicable	1	2.3	1	2.4	1	2.6
Type of surgery						
MVD	7	43.8	7	43.8	7	46.7
MVD and percutaneous procedures	6	37.5	6	37.5	5	33.3

Delphi Survey						
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
MVD and Gamma Knife	1	6.3	1	6.3	1	6.7
Percutaneous procedures	1	6.3	1	6.3	1	6.7
Not sure	1	6.3	1	6.3	1	6.7
Clinicians						
	Round 1		**Round 2**		**Round 3**	
	n	**%**	**n**	**%**	**n**	**%**
Registered	32	100.0	32*	100.0	28	100.0
Completed	31	96.9	28	87.5	26	92.9
Females	19	61.3	17	60.7	16	61.5
Age, years						
<45	13	41.9	11	39.3	10	38.5
45-65	13	41.9	12	42.9	11	42.3
>65	5	16.1	5	17.9	5	19.2
Country of residence						
Denmark	2	6.5	1	3.6	1	3.8
Germany	1	3.2	1	3.6	1	3.8
Ireland	1	3.2	1	3.6	1	3.8
Portugal	2	6.5	2	7.1	2	7.7

Delphi Survey						
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
United Kingdom	24	77.4	22	78.6	20	76.9
United States of America	1	3.2	1	3.6	1	3.8
Clinical experience (years)						
< 5	0	0.0	0	0.0	0	0.0
5-10	5	16.1	4	14.3	3	11.5
>10	26	83.9	24	85.7	23	88.5
Speciality						
General dentist	2	6.5	2	7.1	2	7.7
Oral medicine/Facial Pain physician	11	35.5	10	35.7	10	38.5
Pain specialist	4	12.9	4	14.3	4	15.4
Oral Surgeon	1	3.2	1	3.6	1	3.8
Neurosurgeon	3	9.7	3	10.7	3	11.5
Neurologist	4	12.9	2	7.1	2	7.7
Headache specialist	1	3.2	1	3.6	1	3.8
Clinical psychologist	5	16.1	5	17.9	3	11.5

Delphi Survey						
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
Research experience in the TN field						
Yes	18	58.1	16	57.1	15	57.7
No	13	41.9	12	42.9	11	42.3
Involvement in TN clinical trials						
None	11	61.1	11	68.8	10	66.7
1-3 trials	6	33.3	4	25.0	4	26.7
More than 4 clinical trials	1	5.6	1	6.3	1	6.7
Involvement in TN systematic reviews						
None	12	66.7	12	75.0	11	73.3
1-3 systematic reviews	5	27.8	3	18.8	3	20.0
> 4 systematic reviews	1	5.6	1	6.3	1	6.7
Involvement in other types of TN research						
Guidelines	1	5.6	1	6.3	1	6.7
Book chapter	1	5.6	1	6.3	1	6.7

Delphi Survey						
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
Case series	3	16.7	3	18.8	3	20.0
Clinical study	3	16.7	3	18.8	3	20.0
Genetic and psychometric	1	5.6	1	6.3	1	6.7
TN pathophysiology	2	11.1	2	12.5	2	13.3
Not applicable	7	38.9	5	31.3	4	26.7
Researchers						
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
Registered	7	100.0	6	100.0	6	100.0
Completed	6	85.7	6	100.0	6	100.0
Females	4	66.7	4	66.7	4	66.7
Age, years						
<45	3	50.0	3	50.0	3	50.0
45-65	3	50.0	3	50.0	3	50.0
>65	0	0.0	0	0.0	0	0.0
Country of residence						
Brazil	1	16.7	1	16.7	1	16.7
Denmark	1	16.7	1	16.7	1	16.7

Delphi Survey						
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
Egypt	1	16.7	1	16.7	1	16.7
Italy	1	16.7	1	16.7	1	16.7
United Kingdom	2	33.3	2	33.3	2	33.3
Work in industry/pharma						
Yes	1	16.7	1	16.7	1	16.7
No	5	83.3	5	83.3	5	83.3
Involvement in TN clinical trials						
None	4	66.7	4	66.7	4	66.7
1-3 trials	2	33.3	2	33.3	2	33.3
More than 4 clinical trials	0	0.0	0	0.0	0	0.0
Involvement in TN systematic reviews						
None	2	33.3	2	33.3	2	33.3
1-3 systematic reviews	4	66.7	4	66.7	4	66.7
> 4 systematic reviews	0	0.0	0	0.0	0	0.0

Delphi Survey						
	Round 1		Round 2		Round 3	
	n	%	n	%	n	%
Involvement in other types of TN research (free text)						
Drug development	1	16.7	1	16.7	1	16.7
Observational study	1	16.7	1	16.7	1	16.7
Neurophysiological and neuroimaging	2	33.3	2	33.3	2	33.3
Various	1	16.7	1	16.7	1	16.7
Not applicable	1	16.7	1	16.7	1	16.7

Of the 29 outcomes suggested by participants after round one (list available for consultation in Appendix 4), two were selected by the research team to be included in the two subsequent rounds ("time to return to work/family responsibilities after surgery" and "duration of pain relief"). After three rounds no outcomes met the criteria for exclusion, 17 outcomes met the criteria for inclusion and 23 did not meet consensus. Table 6.2 summarizes the provisionally included and non-consensus outcomes.

Information on how outcomes were scored by each stakeholder group can be seen in Table 6.3. Attrition rates between the mean scores in different rounds are outlined in Appendix 4.

Table 6.2 Provisionally included and non-consensus outcomes after 3 round Delphi

OUTCOMES IN	NO CONSENSUS OUTCOMES
70% or more scored it as a 7-9 and fewer than 15% scored it as 1-3	Definition of either consensus in or consensus Out not met
Access to a specialist TN clinic	Ability to participate in social roles and activities
Coping	Anxiety
Duration of pain relief	Avoidance behaviour
Eating	Catastrophising
Fear of pain or fear of an attack	Depression
Health related quality of life	Effect of TN on family and friends
Literacy of GPs and dentists about TN	Illness beliefs
Overall response to treatment	Intimacy
Pain intensity	Pain free off medication
Pain interference	Pain free on medication
Pain relief	Patient's literacy about TN
Quality of the pain - electric shock	Peer support
Satisfaction with treatment	Quality of the pain - constant burning
Self-care	Reduction in the need for rescue medication
Side effects of medication	Self-efficacy
Side effects of surgery	Self-efficacy on managing chronic conditions
Talking	Self-efficacy on managing emotions
	Social validation
	Social withdrawal and isolation
	Temporal aspects of pain
	Time to return to work/family responsibilities after surgery
	Trigger sensitivity
	Work ability

GP= general practitioner; TN= trigeminal neuralgia

Table 6.3 Scoring of outcomes by stakeholder group – Round 3 of the Delphi survey

Outcomes	Patients n=38								Clinicians n=26								Researchers n=6								
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
	1-3		4-6		7-9		10		1-3		4-6		7-9		10		1-3		4-6		7-9		10		
	Not important		Important but not critical		Critical				Not important		Important but not critical		Critical				Not important		Important but not critical		Critical				
Ability to participate in social roles and activities	0	0.0	4	10.5	34	89.5	0	0.0	0	0.0	2	7.7	24	92.3	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	
Access to a specialist TN clinic	0	0.0	3	7.9	35	92.1	0	0.0	0	0.0	7	26.9	19	73.1	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Anxiety	0	0.0	4	10.5	34	89.5	0	0.0	0	0.0	4	15.4	22	84.6	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	
Avoidance behaviour	2	5.3	15	39.5	20	52.6	1	2.6	0	0.0	5	19.2	21	80.8	0	0.0	0	0.0	4	16.7	5	83.3	0	0.0	
Catastrophising	3	7.9	11	28.9	24	63.2	0	0.0	0	0.0	9	34.6	17	65.4	0	0.0	1	16.7	0	0.0	5	83.3	0	0.0	
Coping	1	2.6	5	13.2	32	84.2	0	0.0	0	0.0	3	11.5	23	88.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Depression	0	0.0	2	5.3	36	94.7	0	0.0	0	0.0	5	19.2	21	80.8	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	
Duration of pain relief	0	0.0	0	0.0	38	100.0	0	0.0	1	3.8	2	7.7	23	83.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Eating	0	0.0	1	2.6	37	97.4	0	0.0	0	0.0	2	7.7	23	88.5	1	3.8	0	0.0	0	0.0	6	100.0	0	0.0	
Effect of TN on Family and friends	2	5.3	8	21.1	27	71.1	1	2.6	0	0.0	16	61.5	10	38.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Fear of pain or fear of an attack	2	5.3	9	23.7	27	71.0	0	0.0	0	0.0	5	19.2	21	80.8	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0	
HRQOL	0	0.0	0	0.0	38	100.0	0	0.0	0	0.0	1	3.8	25	96.2	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Illness beliefs	4	10.5	18	47.4	15	39.5	1	2.6	1	3.8	8	30.8	17	65.4	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	
Intimacy	1	2.6	14	36.8	22	57.9	1	2.6	0	0.0	2	7.7	24	92.3	0	0.0	1	16.7	0	0.0	4	66.7	1	16.7	
Literacy of GPs and dentists about TN	0	0.0	1	2.6	37	97.4	0	0.0	0	0.0	4	15.4	22	84.6	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0	
Overall response to treatment	0	0.0	3	7.9	35	92.1	0	0.0	0	0.0	1	3.8	25	96.2	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0	

Outcomes	Patients n=38								Clinicians n=26								Researchers n=6								
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
	1-3		4-6		7-9		10		1-3		4-6		7-9		10		1-3		4-6		7-9		10		
	Not important		Important but not critical		Critical				Not important		Important but not critical		Critical				Not important		Important but not critical		Critical				
Pain free off medication	0	0.0	5	13.2	32	84.2	1	2.6	2	7.7	9	34.6	15	57.7	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	
Pain free on medication	0	0.0	9	23.7	29	76.3	0	0.0	1	3.8	9	34.6	16	61.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Pain intensity	0	0.0	0	0.0	38	100.0	0	0.0	1	3.8	2	7.7	23	88.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Pain interference	0	0.0	1	2.6	36	94.7	1	2.6	0	0.0	1	3.8	25	96.2	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Pain relief	0	0.0	0	0.0	38	100.0	0	0.0	1	3.8	1	3.8	24	92.3	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0	
Patient's literacy about TN	0	0.0	1	2.6	37	97.4	0	0.0	0	0.0	5	19.2	21	80.8	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	
Peer support	1	2.6	10	26.3	27	71.1	0	0.0	0	0.0	12	46.2	14	53.8	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Quality of the pain - electric shock	1	2.3	0	0.0	37	97.4	0	0.0	1	3.8	5	19.2	20	76.9	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Quality of the pain - constant burning	1	2.3	7	18.4	25	65.8	5	13.2	1	3.8	12	46.2	13	50.0	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	
Reduction in the need for rescue medication	2	5.3	9	23.7	26	68.4	1	2.6	0	0.0	14	53.8	12	46.2	0	0.0	1	16.7	2	33.3	3	50.0	0	0.0	
Satisfaction with treatment	0	0.0	4	10.5	33	86.8	1	2.6	0	0.0	3	11.5	23	88.5	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Self-care	0	0.0	3	7.9	34	89.5	1	2.6	0	0.0	2	7.7	24	92.3	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Self-efficacy	0	0.0	4	10.5	34	89.5	0	0.0	0	0.0	9	34.6	17	65.4	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	
Self-efficacy on managing chronic conditions	0	0.0	5	13.2	33	86.8	0	0.0	0	0.0	8	30.8	18	69.2	0	0.0	0	0.0	1	16.7	4	66.7	1	16.7	
Self-efficacy on managing emotions	0	0.0	8	21.1	30	78.9	0	0.0	0	0.0	8	30.8	18	69.2	0	0.0	1	16.7	1	16.7	4	66.7	0	0.0	
Side effects of medication	0	0.0	3	7.9	35	92.1	0	0.0	1	3.8	3	11.5	22	84.6	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	

Outcomes	Patients n=38								Clinicians n=26								Researchers n=6								
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
	1-3		4-6		7-9		10		1-3		4-6		7-9		10		1-3		4-6		7-9		10		
	Not important		Important but not critical		Critical				Not important		Important but not critical		Critical				Not important		Important but not critical		Critical				
Side effects of surgery	0	0.0	1	2.6	32	84.2	5	13.2	0	0.0	2	7.7	24	92.3	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0	
Social Validation	1	2.6	15	39.5	22	57.9	0	0.0	0	0.0	15	57.7	11	42.3	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Social withdrawal and isolation	5	13.2	10	26.3	22	57.9	1	2.6	0	0.0	5	19.2	21	80.8	0	0.0	0	0.0	1	16.7	5	83.3	0	0.0	
Talking	0	0.0	5	13.2	33	86.8	0	0.0	0	0.0	0	0.0	25	96.2	1	3.8	0	0.0	0	0.0	6	100.0	0	0.0	
Temporal aspects of pain	0	0.0	6	15.8	32	84.2	0	0.0	1	3.8	5	19.2	20	76.9	0	0.0	1	16.7	1	16.7	4	66.7	0	0.0	
Time to return to work/family responsibilities after surgery	1	2.6	12	31.6	20	52.6	5	13.2	1	3.8	11	42.3	13	50.0	1	3.8	0	0.0	3	50.0	3	50.0	0	0.0	
Trigger sensitivity	1	2.6	1	2.6	35	92.1	1	2.6	1	3.8	8	30.8	17	65.4	0	0.0	1	16.7	0	0.0	5	83.3	0	0.0	
Work ability	0	0.0	7	18.4	30	78.9	1	2.6	0	0.0	5	19.2	21	80.8	0	0.0	0	0.0	2	33.3	4	66.7	0	0.0	

Outcomes that reached consensus to be included in the core outcome set, i.e., >70% voted 7-9 and <15% voted 1-3 in all stakeholder groups

Outcomes for which there was no consensus during the e-Delphi, taken forward to discussion at the online consensus meeting

Outcomes voted 7-9 by >70% in each of the stakeholder groups highlighted in grey

n = number; TN: trigeminal neuralgia; HRQOL: health related quality of life; GP: general practitioner

6.5.2 Online consensus meeting

Thirteen participants attended the online consensus meeting (five clinicians, two researchers and six patients) – Table 6.4 includes demographic data of the consensus meeting participants. Twenty-three outcomes which did not meet consensus were informally discussed in breakout rooms. Following discussions, the outcomes were presented for anonymous scoring using the same scoring system as that of the Delphi. Only two outcomes met the criteria for inclusion ("pain free on medication" and "ability to participate in social roles and activities") and were brought forward to the final poll. Of the 19 outcomes provisionally included in the COS, six were deemed "important but not crucial" (Figure 6.2), 11 were deemed "mandatory" to be included in the COS (Figure 6.2), and two reached a tie (quality of the pain – electric shock/access to a specialised TN clinic).

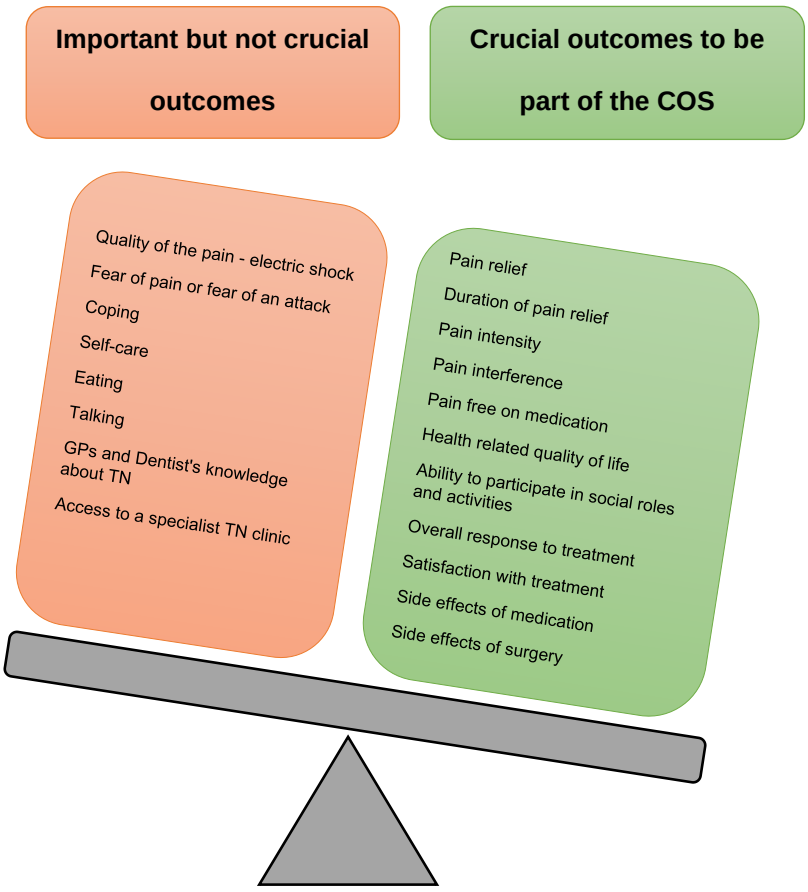

Figure 6.2 Outcomes scored as important *vs* outcomes scored as crucial for inclusion in the COS

Table 6.4 Demographic data of consensus meeting participants

Consensus meeting	N	%
Patients		
Registered	6	100.0
Completed	6	100.0
Females	4	66.7
Age, years		
45-65	4	66.7
>65	2	33.3
Country of residence		
United Kingdom	6	100.0
TN diagnosis		
2-5 years ago	2	33.3
> 5 years ago	4	66.7
Type of pain experienced		
Acute attacks and I always have a background pain (burning; aching)	1	16.6
Acute attacks but I am pain free in between attacks	4	66.7

Consensus meeting	N	%
I am in remission (pain free)	1	16.6
Treatments to date		
Medication only	3	50.0
Medication and surgery	3	50.0
Type of surgery		
MVD	2	
Percutaneous procedures	1	

Clinicians		
	n	**%**
Registered	5	100.0
Completed	5*	100.0
Females	2	40.0
Age, years		
<45	2	40.0
45-65	2	40.0
>65	1	20.0
Country of residence		

Consensus meeting	N	%
Denmark	1	20.0
Germany	1	20.0
United Kingdom	3	60.0
Clinical experience (years)		
>10	5	100.0
Speciality		
Oral medicine/Facial Pain physician	1	20.0
Neurosurgeon	1	20.0
Neurologist	2	40.0
Clinical psychologist	1	20.0
Research experience in the TN field		
Yes	4	80.0
No	1	20.0
Involvement in TN clinical trials		
None	3	60.0
1-3 trials	1	20.0
More than 4 clinical trials	1	20.0

Consensus meeting	N	%
Involvement in TN systematic reviews		
None	3	60.0
1-3 systematic reviews	1	20.0
> 4 systematic reviews	1	20.0
Involvement in other types of TN research (free text)		
Guidelines	2	40.0
Case series	1	20.0
TN pathophysiology	1	20.0
Researchers		
	n	**%**
Registered	2	100.0
Completed	2	100.0
Females	1	50.0
Age, years		
<45	1	50.0
45-65	1	50.0
Country of residence		

Consensus meeting	N	%
Italy	1	50.0
Switzerland	1	50.0
Work in industry/pharma		
Yes	1	50.0
No	1	50.0
Involvement in TN clinical trials		
None	1	50.0
1-3 trials	1	50.0
Involvement in TN systematic reviews		
None	1	50.0
1-3 systematic reviews	1	50.0
Involvement in other types of TN research (free text)		
Drug development	1	50.0
Neurophysiological and neuroimaging	1	50.0

6.6 DISCUSSION

In this Chapter, work which culminated in the development of a TN core outcome set is outlined. Patients, clinicians, and researchers identified 11 outcomes to be used, as a minimum, in future TN clinical trials – pain relief duration of pain relief, pain intensity, pain interference, pain free on medication, health related quality of life, ability to participate in social roles and activities, overall response to treatment, satisfaction with treatment, side effects of medication and of surgery.

This is an important first step in improving outcome measurement and if used widely, will contribute to improved combination and contrasting of results, improved use of research data, and importantly, to improved patient care.

The results presented confirmed, unsurprisingly, that pain dimensions are important in TN as five outcomes relating to pain were included in the COS. The outcome which reached the highest scores was “pain relief”. This is likely to be a good candidate to be the primary outcome in TN research studies, together with “duration of pain relief” outcome. This hypothesis would need further validation.

The burden of TN has been previously reported and a relationship between pain and ability to participate has been identified[101] which is in line with the fact that “ability to participate in social roles and activities” was included in the COS.

There were, however, some unexpected exclusions from the COS, for example, the impact of treatment on mood, specifically anxiety and depression, as the literature supports the understanding that TN pain causes an impact on mental well-being.

During the Delphi survey these outcomes were voted “critical” by more than 70% of participants in two stakeholder groups but not in all three. The same weight was given to all stakeholder groups to account for the disparity in the numbers in each group.

A closer analysis of the Delphi results (Table 6.3) indicates that more than 70% of patients and clinicians scored anxiety as 7-9 but only 66.7% of researchers did. In contrast, catastrophising was scored as 7-9 by more than 70% of researchers but not by more than 70% of clinicians or patients. Catastrophising was defined in the Delphi survey as *"People are said to be catastrophising when they think that the worst will happen"*. This short definition was based on that of the American Psychology association: *"People are said to be catastrophizing when they think that the worst possible outcome will occur from a particular action or in a particular situation or when they feel as if they are in the midst of a catastrophe in situations that may be serious and upsetting but are not necessarily disastrous. The tendency to catastrophize can unnecessarily increase levels of anxiety and lead to maladaptive behaviour."* When the concept of catastrophising is applied in the pain context there are other definitions used such as that by Sullivan: *"an exaggerated negative mental set brought to bear during actual or anticipated painful experience"*. [102] One can hypothesise that the definition presented dictated how the scoring was done, and could have, therefore, contributed to the absence of anxiety from the final COS. In addition, our consensus definition was decided "a priori"; had the cut off been more relaxed, other outcomes could have been considered, but it could also mean that a larger list of outcomes was produced. Anxiety and depression did not reach the cut-off point during the consensus meeting either, which had the advantage of allowing participants to discuss their views on each outcome for which consensus had not been met.

These results contrast with the recommendations made by IMMPACT for inclusion of emotional impact on chronic pain core outcome sets. [86] A possible explanation for this might be the inclusion of the outcome health related quality of life (defined in the Delphi as "An individual's perceived well-being in physical, mental and social aspects of

health") via our Delphi process. Health related quality of life is as a multidimensional concept representing the impact of pain on mental well-being.[568] Similarly, a Core Outcome Set developed for preventative trials of episodic migraines and chronic headaches, did not include outcomes relating to the impact of migraines on mood, and the final list included pain intensity, pain frequency and migraine related quality of life (MRQoL) outcomes. Interestingly, participants in this study chose the Migraine Functional Impact Questionnaire to assess MRQoL which addresses emotional functioning among other domains.[90] This requires further exploration in TN as HRQOL questionnaires have not yet been validated in this patient population. It is also worthwhile acknowledging the prominent role the patients with TN had in this study, in contrast to that of the IMMPACT group. The outcome set recommendations are therefore bound to differ due to the differing stakeholders involved in the respective study methodologies employed.

By including clinicians, researchers and patients in a shared decision-making process, the results reflect the views of many, and their different opinions and perspectives complement each other, contributing to the quality and relevance of the study.[569] Most clinicians had more than 10 years' experience and more than half have research experience in TN. Researchers had participated in clinical trials, systematic reviews and drug development studies, for example (Table 6.1 and Table 6.4). Importantly, 44 patients participated in the Delphi and consensus meeting. As TN is a rare disease, and although consensus processes do not rely on statistical power, having a high number of patients in the study contributes to the generalizability of results. In addition, the international panel of clinicians and researchers able to complete the Delphi and participate in the consensus meeting, reinforced the generalizability of results, although, a case study from a consensus process in gastric cancer, involving 952

participants from 55 countries, concluded that there was little variation in outcome scoring, when considering the region of origin, which is reassuring. [570]

Besides the number of participants, another strength of this study was the low attrition rate of 18.6%. Whilst there is no defined threshold for what is an acceptable attrition rate, based on the guidance for randomised controlled trials, attrition rates >20% can be a source of bias[571]. The differences in the mean scores for each outcome between rounds were, for the majority of outcomes, not statistically significant (Appendix 4), which suggests that, although some participants did not complete the three rounds, attrition bias is not likely to have affected the results[43]

6.6.1 Limitations

Side effects of treatment have been identified as crucial outcomes to be included in the COS, but details on which specific side effects of medication and of surgical procedures were more important to the different stakeholders were not addressed, as this would create an interminable list and could compromise the survey's response rate.

6.7 SUMMARY

This Chapter described the final steps which led to the achievement of this thesis' aim – the development of the COS for TN. This was achieved by involving patients, clinicians and researchers in an iterative and dynamic consensus process, whereby important outcomes to all were identified. The next Chapter will provide an overall discussion of the results achieved and integrate them in the wider TN and chronic pain field context.

CHAPTER 7 GENERAL DISCUSSION

7.1 SUMMARY OF FINDINGS

The aim of this PhD thesis was to develop the core outcome set to be used in clinical trials of trigeminal neuralgia. The aim was achieved, and an 11-outcome set divided across six domain categories was developed by involving patients, their representatives, clinicians, and researchers in a shared decision-making process – Figure 7.1.

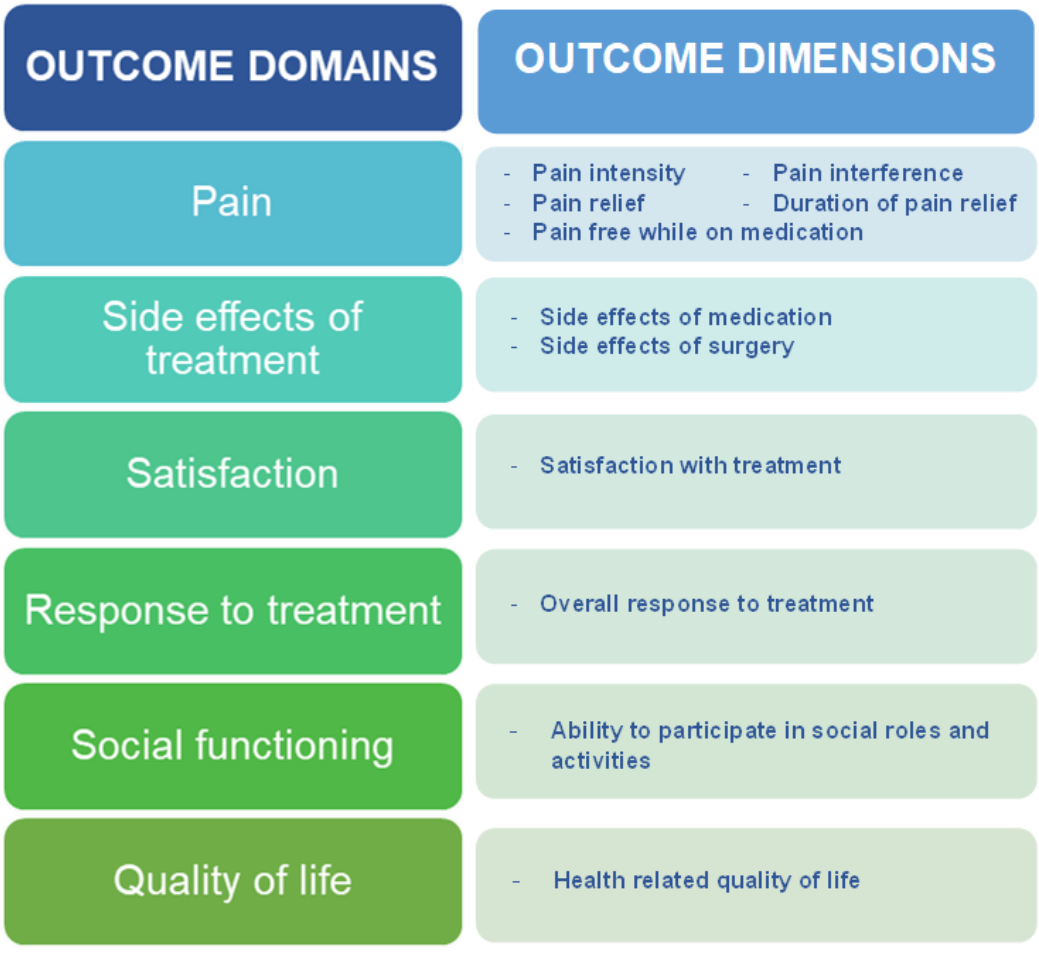

Figure 7.1 Trigeminal Neuralgia Core Outcome Set

The theoretical framework underpinning the present research study was the biopsychosocial model of pain. Although it is clear that pain dimensions are important in TN, outcomes other than pain intensity are also important to assess. The outcomes chosen to be part of the COS are more in keeping with the biopsychosocial model of pain than with the restrictive view that the biological model of pain imposes. [547] A combination of biological outcomes (pain intensity, side effects of treatment), social outcomes (ability to participate in social roles and activities), and psychological outcomes as part of the overarching health related quality of life outcome, is in line with the biopsychosocial model of pain. As with many other types of chronic pain, which can be disruptive to patients and impact on their ability to live a life they value, outcome assessment in TN goes beyond the pain intensity metric.

Research is ongoing to identify the COS for burning mouth syndrome and temporomandibular disorder and data is not yet available to make direct comparisons between the outcomes selected for these conditions and those part of the TN COS however, other chronic pain groups have finalised a COS. Please see Table 7.1 for details on a few examples. There is some overlap between outcomes selected to be part of the TN COS and other chronic pain conditions, such as pain intensity, activity limitation/participation, health related quality of life. Pain frequency is part of the migraine COS however, frequency of pain attacks did not make it to the final group in the TN COS although both conditions can present with intermittent pain attacks. Although participants had access to a definition for each of the outcomes presented in the Delphi, the outcome read “temporal aspects of pain” and not pain frequency. This might have not been clear to those completing the survey and it might justify why it did not reach consensus for inclusion.

Table 7.1 Core outcome sets developed for different chronic pain conditions

	Chronic regional pain syndrome[97]	Pelvic girdle pain[572]	Chronic and episodic migraine[90]	Multimodal pain therapy[573]
Outcome Domains	Pain Disease severity Participation/ physical function Emotional/ psychological function Self-efficacy Catastrophising Patient global impression of change	Pain frequency Pain intensity Pain severity Activity limitation Function Disability Health related quality of life Fear avoidance	Pain intensity Pain frequency Migraine related quality of life	Pain intensity Pain frequency Physical activity Emotional wellbeing Satisfaction with social roles and activities Productivity Health-related quality of life Patient's perception of treatment goal achievement

Arguably, if there was a curative treatment for TN pain, or for any other type of chronic pain, then other outcomes would probably not matter. As illustrated in Table 1.1 in Chapter 1, some surgical treatment options provide long term pain relief, but there are cases in which, despite surgery, the pain remains.[5] Equally, in cases where patients experience persistent concomitant pain, likely explained by central sensitization mechanisms, oftentimes, it cannot be resolved by medical/surgical treatment. Until there is a curative treatment, other dimensions of pain cannot and should not be disregarded. The results achieved in the present work reiterate this argument.

In comparison with the results obtained in Chapter 3, which were mapped to the IMMPACT core domains[86], the TN COS aggregates more dimensions of pain and adds the “ability to participate in social roles and activities” dimension. This last dimension was thoroughly discussed by patients as outlined in Chapter 5. Due to the recurrent and unpredictable nature of TN, this is an important construct to assess. This is of course rather specific to a recurrent pain type in contrast with a more continuous one, hence the importance of investigating outcomes that matter to specific pain populations, and not generalise the use of outcomes for all pain types.

A study by Zidarov aimed at identifying the core patient reported outcome domains for routine clinical care in chronic pain reports that recreation and leisure (e.g. sports, social and family activities) were among the most highly nominated areas of participants' lives which were affected by chronic pain and those that participants would like to improve. [574] These results are in line with those obtained in the present study and support the use of the biopsychosocial model as a framework to interpret the experience of chronic pain. A recent European survey of 487 chronic pain patients identified that their main goals were: pain reduction (91.2%), taking part in family and social activities (72.5%) and household tasks (68.1%).[558] Despite this evidence, information on the impact of chronic pain on the social domain of health is seldom reported. [116] During the Delphi survey, pain relief was the outcome which reached the highest scores by the three stakeholder groups. Although not by a large amount, those scoring thought of this outcome slightly more important than pain intensity. Pain intensity, some argue, might be the wrong metric for assessment of chronic pain and to drive its treatment.

In contrast to the IMMPACT core domains[86], consensus was not reached for inclusion of anxiety and depression on the TN COS, however, HRQOL was. The IMMPACT group includes HRQOL in the "physical function" domain, however, assessing HRQOL involves assessment of physical, mental, and social well-being. The importance of psychological well-being on chronic pain cannot be ignored and is of crucial importance. Although, anxiety and depression domains were not specifically included in the TN COS, arguably these must be assessed when looking at what questionnaires to use in the COS, a HRQOL questionnaire is chosen.

During the focus group work which preceded the consensus stages, patients were clear and adamant on how crucial a timely and adequate referral to a specialist was

to their lived experience with TN. This was validated during the Delphi by the high level of importance attributed to “Access to a specialist clinic” and “Literacy of GPs and dentists about TN” by all stakeholder groups as seen by these outcome’s mean scores (Appendix 4). A retrospective appraisal of the results has highlighted that perhaps these non-clinical outcomes should not have been added to the list used in the Delphi survey so as not to create misinterpretation of the study’s aim. Although these non-clinical outcomes would not traditionally be included in a clinical trial it can be argued that in the case of TN, their importance deserves at least some consideration. Firstly, it was important to acknowledge these outcomes as they reflect patients’ unmet needs, which is good practice in any patient centred research[575] and a specific recommendation of the COMET initiative in COS development. Secondly, recruitment and retainment of patients in clinical trials is a difficult task, especially in the context of a rare disease. [79, 576] Improving the knowledge of primary care clinicians about a disease not only gives patients better chances of an adequate care pathway, but GPs may play a fundamental role in motivating and supporting patients to participate in clinical trials. [576] Although treatment might be started in more specialised settings, patients’ GPs will continue to be involved and provide support to this cohort of patients, and some patients might even be discharged to their care, once stable. [6] GP appreciation of the need for further clinical research in this field would be important to encourage patients to participate in clinical research.

Finally, the work described in Chapter 4 confirms how the field of TN has not been engaged in making sure the outcomes are assessed in a correct and valid way. Perhaps the explanation for this is due to the lack of involvement of those with knowledge of psychometrics in TN research. A multidisciplinary group is as important in research as it is in clinical practice and there is increasing awareness of the need

to have a multidisciplinary approach to the clinical management of TN. [107, 108] The results outlined in Chapter 4 are the starting point of what lies ahead, the identification and validation of questionnaires to be used with each outcome in the COS.

7.2 STRENGTHS AND LIMITATIONS

This was the first time that a core outcome set was developed for TN. As described in Chapter 2, guidance from the COMET group was followed. Support available on the COMET webpage via the COMET handbook, access to published or ongoing methodological studies on COS development, availability of plain language resources to use with the patient cohorts and the opportunity to use the Delphi manager software favoured the use of the methodology endorsed by this group. It is important to acknowledge however, that there are several groups working in the field of COS development. In addition to COMET (Core Outcome Measures in Effectiveness Trials - www.COMET-initiative.org), groups such as ICHOM (International Consortium for Health Outcomes Measurement – www.ichom.org) and regulatory bodies such as the FDA have advocated for the development of COS. Collaborative approaches between some of these groups has already begun (The Red Hat group[577]) which will be essential as the field evolves.

Efforts have been made to ensure that those for whom the COS matters the most were involved. [566] The number of patients involved is a particularly important strength of the present work. Given that TN is a rare condition, involving 58 patients throughout the different stages contributes to the generalisability of the study's results. The patient cohort included those in pain (with and without continuous concomitant pain), those in remission, those who had tried medication only, and those who had tried medicines

and surgery – classical and idiopathic TN. Patients with secondary TN were not recruited, but this was purely by chance. Although it is anticipated that their pain experience is similar and their opinions about outcomes of treatment the same, their preferences have not been identified. Most of the TN phenotypes were represented throughout the study.

Most of those in the patient/patient representatives' cohort were from the United Kingdom where access to health care is free. Other healthcare systems around the globe might provide different patient experiences and patients might be more or less willing to participate in research due to local and cultural differences. [578] Notwithstanding, a survey done among 249 facial pain patients (94% suffering with TN), participating in patient led conferences in the UK (n=70), USA (n=144) and Australia (n=35) suggests that their views are similar. Patients were asked to rate, on a Likert scale (0-10), what their expectations for the conference were. The highest rankings were those attributed to improving their knowledge about their pain condition (mean = 9.6; SD=1.0), improving their ability to make decisions about their care (mean=9.3; SD=1.8), to feel in control (mean=8.7, SD=2.3) and to find out about ways of improving their HRQOL (mean=8.7, SD=2.3). [579] In contrast, a systematic review of international representation of patients in Delphi surveys gives examples of studies where the prioritisation of certain outcomes differed, depending on the country of origin of the participants. However, in these studies, these outcomes did not make it to the final COS. The same systematic review identified a study in pancreatic cancer, where the final COS would have been different if outcomes had been analysed by continent and not as a whole cohort. [580] These examples illustrate that one should not assume that patients from different geographic locations will definitely rank outcomes in a similar way.

While the participation of patients in the present work can be considered highly valuable, generalisation to patient population's outside of the UK needs to be done with caution.

Seeing that their views were as important as those of the professionals may have encouraged patients to volunteer more ready to the planning of future research studies as well as being participants. The NIHR (National Institute for Health and Care Research) insist that patients are active participants in the design of studies they sponsor as better public involvement leads to better health and social care research. [581]

Many of the authors with the highest TN research outputs were involved and contributed to the results of the present study. [582] This was an international cohort of clinicians and researchers and by involving them in the identification of important outcomes, it is therefore more likely that these participants will utilise and endorse the TN COS in future studies. Although the number of those identifying mainly as researchers was small, some of the clinicians participating were also researchers.

Due to the COVID 19 pandemic, the focus group work and the consensus meeting had to be conducted online. This was a positive experience for all involved, based on informal feedback from participants, but it is likely that non-verbal communication was lost. [583] Additionally, those attending were familiar with the use of online/digital technology. Digital skills were required to obtain consent (for which an electronic signature was needed) and for the use of the online meeting software. Some patients declined participation in the focus group since the study had to be carried out online. These issues have been highlighted by others conducting online qualitative research. [584] The requirement for digital literacy may have biased the sample toward those in

particular socio-economic groups/younger populations. Studies conducted online have the advantage of including participants from geographically diverse areas, but can exclude those not familiar with technology, usually older generations. [585] This is also supported by data from the Organisation for Economic Co-Operation and Development (OECD), comparing younger and older generation use of the internet (in 2019, over 95% of 16–24-year-olds in the OECD *vs* 71% of 65-74-years-olds, used the internet). [586]

Data retrieved in Chapters 3 and 4 were limited to English studies therefore the results might be biased. The experience of pain is influenced by many individual factors such as language, culture, and ethnicity. These individual factors might influence pain prevalence, pain severity levels, pain perception, pain related beliefs and ability to cope with pain. This will, no doubt, influence the type of data collected in clinical studies and how this data might be assessed and interpreted via patient reported outcome measures. A study by Cruz Almeida and colleagues[587], looking at experimental and clinical pain sensitivity and pain inhibition outcomes in older African Americans and in non-Hispanic white patients with knee osteoarthritis, concluded that the racial and ethnical differences could account for differences in those outcomes. Greater pain severity was found in the African American group compared to the non-Hispanic group. Patients in minority groups are at higher risk of having less access to healthcare and therefore their pain might be undertreated which can contribute to higher pain levels/severity. [588]

CHAPTER 8 RECOMMENDATIONS FOR FUTURE WORK

The initial steps to improve outcome assessment in TN have been taken, but the work presented in this thesis is not sufficient on its own. There are many more avenues that need to be pursued, that can ultimately improve the lives of those living with TN.

The development of a core outcome set is an important step towards improving harmonisation of research results which will inevitably have direct clinical implications, for example, helping patients and clinicians in their decision making processes. [43] Future trialists may decide to use additional outcomes, for example, anxiety, depression or fear of a painful attack, but a justification for not using the suggested COS must be available so that conclusions can be drawn about its validity and need for modification.

8.1 RECOMMENDATIONS FOR FUTURE RESEARCH

One of the factors that contributes to the uptake of a COS is providing researchers not only with the "what to measure" information, but also with "how to measure" details. [43] Others have already followed on from the identification of the domains for a COS to recommending which questionnaires to use for the outcome assessment. Examples exist in the fields of chronic/episodic migraine[90], complex regional pain syndrome[97] and work is underway to identify outcome measures for patients with burning mouth syndrome. [123]

Building directly on the thesis results, work will be conducted to identify what questionnaires are valid, reliable, and responsive to be used in research studies of TN, in accordance with guidance provided by the COnsensus-based Standards for the

selection of health Measurement Instruments (COSMIN) group.[69, 589] As little evidence exists in terms of the validity of questionnaires, a body of work needs to be done to validate questionnaires to be used in TN. For example, the Penn-FPS-R has promising content validity results, but it needs further investigation of its internal structure and responsiveness, as seen in Chapter 4.

Future validation studies of this core outcome set by other research groups, especially those from outside the UK would be welcomed. The UK has a unique healthcare system, and patients from other countries might have different type of expectations about research and clinical care. In addition to cultural variations[580], economic factors might also play a role in the prioritising of outcomes.[459]

Another area of future research would be to explore in detail the specific side effects of the different treatments and their place in the TN core outcome set. Core outcome sets are not static and are supposed to be reviewed periodically; outcomes which have been included might be removed and future research might indicate that other outcomes should be included.

It is of utmost importance that the COS is implemented in future research studies. Hughes and colleagues systematically reviewed data retrieved from studies investigating the uptake of COS in RCTs (n=24) and systematic reviews (n=2) and identified that the main barriers for the uptake of COS were lack of awareness by those conducting research, perception of increased patient burden, mismatch between outcomes in a COS and those preferred by trialists, and lack of information on how to assess the outcomes.[590] Implementation of a COS benefits from endorsement, for example by funding bodies[591], journal editors[592], professional bodies, regulatory bodies (e.g., FDA and EMA), guideline developers (e.g., NICE - The National Institute

for Health and Care Excellence), patient organisations, and systematic reviewers (e.g., Cochrane). [593] In fact, the Cochrane Handbook for systematic reviews of interventions already recommends the use of a COS - '*where available, established sets of core outcomes should be used*'. [594]

It is expected that publications arising from the present work, as well as conference presentations, social media publicity and the involvement of a patient association (TNA UK) are useful strategies to promote the existence and uptake of the TN COS. It is hoped that the TN COS will become as visible as possible to those involved in research and that it proves to be a contributing tool to the success of TN research studies.

8.2 RECOMMENDATIONS FOR CLINICAL PRACTICE

The use of a TN COS in clinical trials will provide more standardized data which can be aggregated by systematic reviewers and those conducting meta-analysis. Data can then be used to create evidence-based guidelines for the management of TN in clinical practice. As TN can be managed by different healthcare professionals (e.g., dentists, neurosurgeons, neurologists, pain specialists, GPs, oral medicine physicians), clinical guidelines will be crucial to allow patients to have access to standardised and universal care, which means that more patients will have access to adequate treatment regardless of their geographical location or clinical care setting. [595] Furthermore, the use of evidence based guidance can reduce the use of inadequate treatments for TN, for example opioids. Although no evidence exists for the use of this group of drugs in the management of TN or neuropathic pain[596], many patients are still being prescribed opioids. [597] [598]

The qualitative work done with patients gave rise to rich data which would be worth reanalysing. New insights could be gained to develop a conceptual framework for TN which could be used to inform the design of future research studies. [599] Many of the constructs important to the patients have been identified as outcomes but others could act as disease modifiers (e.g., predictors, amplifiers, modulators). For example, fear avoidance behaviour has been linked to increased disability in those suffering with low back chronic pain[600], and poor sleep has been associated with lowering pain thresholds and as a risk factor for the development of chronic pain. [601, 602] If the many identified constructs were further explored in TN, data collected in the clinical setting could inform future research studies and if the relationships were confirmed, multidisciplinary treatment could target those constructs which are modifiable (such as fear, coping strategies, catastrophising etc.). [107, 108]

CHAPTER 9 CONCLUSION

Outcome assessment in clinical trials is as crucial as it is challenging, more so when the disease under study is rare. The findings of the present thesis have led to the development of an 11-item core outcome set, which will minimise some of the challenges associated with outcome assessment in TN.

The systematic review of the literature on what outcomes have been used to date and how these have been assessed was the baseline of this study. It confirmed the need to improve the knowledge on what the important outcome domains are in TN, and the urgent need to improve outcome assessment. The qualitative work conducted with patients gave rise to insights about their lived experience, and identified what outcomes are important to them; these were later presented during the consensus processes. Finally, the partnership between patients, clinicians and researchers during the consensus processes led to the development of the core outcome set, the primary aim of the project. Although there are different methodological approaches to the development of a COS, the TN COS includes outcomes that were identified in all stages of the project, confirming that, for this specific case, the methods were correctly chosen.

The future implementation of this COS will contribute to a more transparent, systematic, and rigorous reporting of research results. It will also improve communication with patients, enabling them to anticipate and understand the consequences of their illness and of their treatment. Those most affected by TN will find it easier to decide which treatment to choose, ultimately improving their healthcare journeys and their lives.

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APPENDICES

APPENDIX 1 – Chapter 3

Search strategy for MEDLINE AND EMBASE

Embase and Medline search strategy: surgical procedures 2008-October 2019

Set#	Searched for	Results
S1	MESH.EXACT("Trigeminal Neuralgia") OR EMB.EXACT("trigeminus neuralgia")	17890*
S2	tio,ab(tic near/1 do*lo*re*ux*) or tio,ab(trigemin[*2] near/1 neuralg*)	13747*
S3	mesh(su) OR emb(su)	3911309*
S4	MESH.EXACT.EXPLODE("Nerve Block") OR EMB.EXACT.EXPLODE("nerve block")	61010*
S5	MESH.EXACT("Rhizotomy") OR EMB.EXACT.EXPLODE("rhizotomy")	3330°
S6	MESH.EXACT("Microvascular Decompression Surgery") OR EMB.EXACT("microvascular decompression")	1320°
S7	MESH.EXACT.EXPLODE("Decompression, Surgical") OR EMB.EXACT.EXPLODE("decompression surgery")	77205*
S8	MESH.EXACT("Radiosurgery") OR EMB.EXACT("gamma knife radiosurgery") OR EMB.EXACT("stereotactic radiosurgery") OR EMB.EXACT("radiofrequency ablation") OR EMB.EXACT.EXPLODE("radiosurgery")	78450*
S9	MESH.EXACT.EXPLODE("Stereotaxic Techniques") OR EMB.EXACT.EXPLODE("stereotactic procedure")	72939*
S10	MESH.EXACT.EXPLODE("Denervation") OR EMB.EXACT.EXPLODE("neurectomy") OR EMB.EXACT.EXPLODE("denervation")	111427*
S11	MESH.EXACT.EXPLODE("Neurosurgical Procedures") OR MESH.EXACT("Neurosurgery") OR EMB.EXACT.EXPLODE("nerve surgery") OR EMB.EXACT.EXPLODE("neurosurgery")	471377*
S12	MESH.EXACT.EXPLODE("Electrocoagulation") OR EMB.EXACT("electrocoagulation") OR EMB(radiofrequency)	78744*
S13	EMB.EXACT("balloon dilatation")	18067*
S14	mesh(rt) or emb(rt)	495191*
S15	MESH.EXACT.EXPLODE("Radiotherapy") OR EMB.EXACT.EXPLODE("radiotherapy")	738380*
S16	MESH.EXACT("Glycerol") OR EMB.EXACT("glycerol")	69765*
S17	EMB.EXACT("ablation therapy") OR MESH.EXACT("Ablation Techniques")	20763*
S18	EMB.EXACT.EXPLODE("nerve stimulation") OR MESH.EXACT.EXPLODE("Electric Stimulation Therapy") OR EMB.EXACT.EXPLODE("electrostimulation")	280892*
S19	tio,ab("microvascular decompression" or "micro vascular decompression" or MVD or "partial nerve section" or neurectom* or rhizotom* or neurosurg* or radiofrequency or rhizolysis or gangliolysis or percutaneous or microcompression or "micro compression" or "balloon compression" or "posterior fossa surgery" or gammaknife or "gamma knife" or stereota*ic or cyberknife or "cyber knife" or radiosurg* or "radiation therapy" or radiotherap* or "radiation treatment" or glycerol or ablative or ablation or (peripheral near/2 (block* or stimulation)) or LINAC or "linear accelerator" or "nerve block*")	1404979*
S20	**(s1 or s2) and (s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19) and pd(2008-2019) and la(English)**	**3035°**
S21	**S20 and ud(>20181231)**	**106***

Embase and Medline search strategy: medical treatment 1946 - October 2019

Set#	Searched for	Results
S1	MESH.EXACT("Trigeminal Neuralgia") OR EMB.EXACT("trigeminus neuralgia")	17890*
S2	tio,ab(tic near/1 do*lo*re*ux*) or tio,ab(trigemin[*2] near/1 neuralg*)	13747*
S3	MESH.EXACT("Baclofen") OR EMB.EXACT("baclofen") OR subst("baclofen") OR (baclofen or baclofene or atrofen or "ba 34647" or ba34647 or backen or baclan or baclapone or baclo or baclon or baclophen or baclosal or baclospas or bacofen or bacron or bafen or baklofen or baropan or bigafen or "ciba 34647" or "ciba 34647ba" or ciba34647 or ciba34647ba or clofen or curofen or espast or gablofen or genpharm or intralcal or kemstro or lebic or lioresal or lioresyl or liotec or lyflex or miorel or nubaclo or onelaxant or pacifen or spinax or stelax)	26142*
S4	MESH.EXACT("Carbamazepine") OR EMB.EXACT("carbamazepine") OR subst("carbamazepine") OR (carbamazepin or carbamazepine or amizepin or amizepine or atretol or biston or calepsin or camapine or carbadac or carbagen or carbategral or carbatol or carbatrol or carbazene or carbazep or carbazepin or carbazina or carmaz or carnexiv or carpaz or carzepin or carzepine or clostedal or convuline or epileptol or epimax or epitol or eposal or equetro or "espa lepsin" or espalepsin or finlepsin or foxalepsin or "g 32883" or g32883 or hermolepsin or karbamazepin or kodapan or lexin or mazepine or mazetol or neugeron or neurotol or neurotop or nordotol or panitol or servimazepin or sirtal or "spd 417" or spd417 or tardotol or taver or tegol or tegral or tegretal or tegretol or tegrital or telesmin or "temporal slow" or temporol or teril or timonil)	100355*
S5	EMB.EXACT("fosphenytoin sodium") OR subst("fosphenytoin") OR (fosphenytoin or phosphenytoin or "acc 9653" or acc9653 or cerebyx or "ci 982" or ci982 or "pro epanutin" or proepanutin or prodilantin)	2109°
S6	MESH.EXACT("Gabapentin") OR EMB.EXACT("gabapentin") OR subst("gabapentin") OR (gabapentin or "ci 945" or ci945 or dineurin or gabalept or "gabaliquid geriasan" or gabatin or gantin or "go 3450" or go3450 or "goe 3450" or goe3450 or gralise or kaptin or keneil or neurontin or neurotonin or nupentin)	34894*
S7	MESH.EXACT("Lamotrigine") OR EMB.EXACT("lamotrigine") OR subst("lamotrigine") OR (lamotrigin or lamotrigine or "bw 430 c" or "bw 430c" or "bw 430c78" or bw430c or bw430c78 or crisomet or labileno or lamepil or lamictal or lamictin or lamodex or lamogine or lamotrix or neurium)	29025*
S8	MESH.EXACT("Lidocaine") OR EMB.EXACT("lidocaine") OR subst("lidocaine") OR (lidocain or lidocaine or aeroderm or akten or alphacain or alphacaine or anestacain or anestacaine or anestacon or anestacone or aritmal or astracain or astracaine or betacain or betacaine or cidancain or cidancaina or cidancaine or "corus 1030" or corus1030 or cuivasil or dalcain or dalcaine or dentipatch or "dequa spray" or dequaspray or dolicain or dolicaine or "dube spray" or dubespray or duncain or duncaine or dynexan or "ela max" or elamax or esracain or esracaine or farmacain or farmacaina or farmacaine or gesicain or gesicaine or glydo or gravocain or gravocaine or isicain or isicaine or jetokain or "l cain" or "l caine" or "laryng o jet" or laryngojet or lecasin or leostesin or "lida mantle" or lidamantle or lidocaton or lidocor or lidocorit or lidoderm or lidoject or lidonest or lidopain or lidopen or lidothesin or lignocain or lignocaine or lignostab or lincain or lincaine or liquocain or liquocaine or "ll 30" or ll30 or "lmx 4" or lmx4 or "lmx 5" or lmx5 or "lta ii" or ltaii or maricain or maricaine or "neo lidocaton" or "neo novutox" or neolidocaton or neonovutox or octocain or octocaine or otipax or penles or remicain or remicaine or restylane or roxicain or roxicaina or roxicaine or rucain or rucaina or rucaine or ruciana or solarcain or solarcaine or solcain or solcaine or truxacain or truxacaine or "uad caine" or uadcaine or vasocain or vasocaine or versatis or xidocain or xidocaine or xiline or xilocain or xilocaina or xilocaine or xilonest or xilotane or xilyne or xylcain or xylcaine or xylestesin or xylesthesin or xylocain or xylocaina or xylocaine or xylocard or xylocitin or xyloctin or xyloneural or xylonor or xyloproct or xyloton or xylotox or xylyne or zingo or ztlido)	111073*
S9	MESH.EXACT("Oxcarbazepine") OR EMB.EXACT("oxcarbazepine") OR subst("oxcarbazepine") OR (oxcarbazepin or oxcarbazepine or apydan or "co 36006" or co36006 or "gp 47680" or gp47680 or oxocarbazepin or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trileptin)	12206*
S10	MESH.EXACT("Phenytoin") OR EMB.EXACT("phenytoin") OR subst("phenytoin") OR (phenytoin or phenytoine or alepsin or aleviatin or antilepsin or antisacer or cansoin or citrullamon or comital or cumatil or danten or dantoin or denyl or difenin or difetoin or differenin or difhydan or "di hydan" or dihydan or dilantin or dintoin or dintoina or diphantoin or diphantoine or diphedal or diphedan or diphenin or diphenine or diphentoin or "diphenyl	84919*

	hydantoin" or diphenylhydantoin or "di phen" or diphen or diphenylan or diphenyldantoin or diphenytoin or ditoin or ditomed or ekko or epamin or epanutin or epelin or epilan or epilantin or epileptin or eptal or eptoin or felantin or fenantoin or fenatoin or fenidantoin or fenitoin or fenytoin or fenytoine or hidanil or hidantal or hydantin or hydantinal or hydantoinal or hydantol or idantoin or lehydan or lepitoin or minetoin or neosidantoina or phenhydan or phenhydane or phenilep or phentytoin or phentytoine or phenytoinum or phenytonium or phenybin or phenydan or phenydantin or phenytek or phenytex or pyoredol or sanepil or sodantoin or sodanton or solantoin or solantyl or tacosal or vasilcon or zentropil)	
S11	MESH.EXACT("Pimozide") OR EMB.EXACT("pimozide") OR subst("pimozide") OR (pimozid or pimozide or antalon or opiran or orap or pimocide or pimoride or pinozide or pizide or "r 6238" or r6238)	10702*
S12	MESH.EXACT("Pregabalin") OR EMB.EXACT("pregabalin") OR subst("pregabalin") OR (pregabalin or "3 isobutyl gaba" or "3 isobutylgaba" or "ci 1008" or ci1008 or lyrica or "pd 144723" or pd144723)	15954*
S13	MESH.EXACT("Ropivacaine") OR EMB.EXACT("ropivacaine") OR subst("ropivacaine") OR (ropivacaine or ropivacain or ropivacaina or "al 381" or al381 or "lea 103" or lea103 or narop or naropein or naropeine or naropin or naropina)	15414*
S14	**(s1 or s2) and (s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13) and la(English)**	**2575°**
S15	**S14 and ud(>20181231)**	**102***

Data extraction code

1st code: Exclusion and Inclusion – SCREENING

- INCLUDE based on cohort and treatment [Include]
  Studies with a TN cohort >10 patients >18 years of age undergoing medical or surgical treatment, or both.
- EXCLUDE Not TN [Exclude]
- EXCLUDE Cohort < 18years [Exclude]
- EXCLUDE Cohort < 10 patients [Exclude]
- EXCLUDE Systematic reviews and protocols [Exclude]
  all systematic reviews, protocols of RCT, meta-analysis, pilot studies
- EXCLUDE Not intervention studies [Exclude]
- EXCLUDE Full text not available [Exclude]
- EXCLUDE conference abstract/conference proceedings/editorials/comments [Exclude]
- EXCLUDE Full text not in English [Exclude]
- EXCLUDE Technical papers [Exclude]
- EXCLUDE Animal studies [Exclude]

2nd code: DATA EXTRACTION from the <u>included</u> references

- TN COHORT [Not selectable (no checkbox)]
  - Classic TN [Selectable (show checkbox)]
  - Idiopathic TN [Selectable (show checkbox)]
  - Secondary to Neurological disease [Selectable (show checkbox)]
    - Multiple sclerosis [Selectable (show checkbox)]
    - Tumours [Selectable (show checkbox)]
  - Mixed cohort [Selectable (show checkbox)]
  - Not specified [Selectable (show checkbox)]
  - Other [Selectable (show checkbox)]
  - Burchiel classification [Selectable (show checkbox)]

- DATA COLLECTION [Not selectable (no checkbox)]
  - Prospective [Selectable (show checkbox)]
  - Retrospective [Selectable (show checkbox)]
  - Not specified [Selectable (show checkbox)]
  - Combined [Selectable (show checkbox)]
- INTERVENTION [Not selectable (no checkbox)]

- Medical [Selectable (show checkbox)]
- Surgical [Selectable (show checkbox)]
- Mixed [Selectable (show checkbox)]
  compare medical and surgical

- OUTCOME DOMAIN [Not selectable (no checkbox)]
  - PAIN [Selectable (show checkbox)]
    - Pain intensity [Selectable (show checkbox)]
      - Visual analogue scale (VAS) [Selectable (show checkbox)]
      - Verbal numeric pain scale (VNPS) [Selectable (show checkbox)]
      - Verbal Pain Scale (VPS) [Selectable (show checkbox)]
      - Brief Pain Inventory (BPI) [Selectable (show checkbox)]
      - McGill Pain Questionnaire [Selectable (show checkbox)]
      - Barrow Neurological Institute Pain Intensity Score (BNI) [Selectable (show checkbox)]
      - Numeric Rating Scale (NRS) [Selectable (show checkbox)]
      - Qualitative pain descriptors [Selectable (show checkbox)]
        Mild, moderate, severe or similar qualitative descriptors
      - No outcome measure [Selectable (show checkbox)]
      - Other [Selectable (show checkbox)]
    - Pain relief [Selectable (show checkbox)]
      - Visual analogue scale (VAS) [Selectable (show checkbox)]
      - Verbal Pain Scale (VPS) [Selectable (show checkbox)]
      - Burchiel classification [Selectable (show checkbox)]
      - Numeric rating scale (NRS) [Selectable (show checkbox)]
      - Barrow Neurological Institute Pain Intensity Score (BNI) [Selectable (show checkbox)]
      - Modified BNI [Selectable (show checkbox)]
      - Marseille Scale [Selectable (show checkbox)]
      - MVD Evaluation Score [Selectable (show checkbox)]
      - Likert scale [Selectable (show checkbox)]
      - Regis classification of efficacy of treatment [Selectable (show checkbox)]
      - Other [Selectable (show checkbox)]
      - No outcome measure [Selectable (show checkbox)]
        - Pain reported in percentage, KM, OR, CI, p value [Selectable (show checkbox)]
          - Other [Selectable (show checkbox)]

- Pain frequency [Selectable (show checkbox)]
  - Pain diary [Selectable (show checkbox)]
  - The Constant Face Pain Questionnaire [Selectable (show checkbox)]
  - No outcome measure [Selectable (show checkbox)]
  - Pain vector diagram [Selectable (show checkbox)]
- Duration of pain free/time to recurrence [Selectable (show checkbox)
  - No outcome measure [Selectable (show checkbox)]

- PHYSICAL FUNCTIONING [Selectable (show checkbox)]
  - Quality of life [Selectable (show checkbox)]
    - SF-36 [Selectable (show checkbox)]
    - EQ-5D [Selectable (show checkbox)]
    - BPI [Selectable (show checkbox)]
    - BPI facial [Selectable (show checkbox)]
    - WHOQOL-100 [Selectable (show checkbox)]
    - SF-12 [Selectable (show checkbox)]
    - Sickness Impact Profile [Selectable (show checkbox)]
    - Other [Selectable (show checkbox)]
    - No outcome measure [Selectable (show checkbox)]
  - Disability [Selectable (show checkbox)]
    - Pain disability index [Selectable (show checkbox)]
  - Pain interference [Selectable (show checkbox)]
    - BPI facial [Selectable (show checkbox)]
  - Ability to work [Selectable (show checkbox)]
    - Likert scale [Selectable (show checkbox)]
    - Self-perceived productivity scale [Selectable (show checkbox)]
  - Daily activities [Selectable (show checkbox)]
    - Activity of Daily living [Selectable (show checkbox)]
    - Penn Facial Pain Scale [Selectable (show checkbox)]
    - Other [Selectable (show checkbox)]
    - No outcome measure [Selectable (show checkbox)]

- EMOTIONAL FUNCTIONING [Selectable (show checkbox)]
  - Anxiety [Selectable (show checkbox)]

        - Beck Anxiety Inventory (BAI) [Selectable (show checkbox)]
        - Hamilton Anxiety Scale (HARS) [Selectable (show checkbox)]
    - Depression [Selectable (show checkbox)]
        - Beck Depression Inventory (BDI) [Selectable (show checkbox)]
        - Hamilton Depression (HDRS) [Selectable (show checkbox)]
        - Patient Health Questionnaire-9 (PHQ9) [Selectable (show checkbox)]
    - Anxiety and Depression [Selectable (show checkbox)]
        - Hospital Anxiety and Depression Scale (HADS) [Selectable (show checkbox)]
        - Other [Selectable (show checkbox)]
        - No outcome measure [Selectable (show checkbox)]
    - Catastrophising [Selectable (show checkbox)]
        - Pain Catastrophising Scale (PCS) [Selectable (show checkbox)]

- PARTICIPANT RATING OF IMPROVEMENT AND SATISFACTION WITH TREATMENT [Selectable (show checkbox)]
    - Patient global impression of change [Selectable (show checkbox)]
    - Patient satisfaction scale (PSS) [Selectable (show checkbox)]
    - Satisfaction - Likert scale [Selectable (show checkbox)]
    - VAS [Selectable (show checkbox)]
    - Other [Selectable (show checkbox)]
    - No outcome measure [Selectable (show checkbox)]

- SYMPTOMS AND ADVERSE EVENTS [Selectable (show checkbox)]
    - Medical treatment [Selectable (show checkbox)]
        - Liverpool AEP [Selectable (show checkbox)]
        - AEP [Selectable (show checkbox)]
        - ABNAS [Selectable (show checkbox)]
        - No adverse events [Selectable (show checkbox)]
        - Cognitive impairment [Selectable (show checkbox)]
        - Hyponatraemia [Selectable (show checkbox)]
        - Ataxia [Selectable (show checkbox)]
        - Abnormal liver function [Selectable (show checkbox)]
        - Bone marrow disfunction [Selectable (show checkbox)]
        - Cutaneous reactions [Selectable (show checkbox)]
        - Dizziness [Selectable (show checkbox)]
        - Drowsiness [Selectable (show checkbox)]

        - Allergic reaction (not specific) [Selectable (show checkbox)]
        - Gastrointestinal (nausea, vomiting) [Selectable (show checkbox)]
        - Other (weight gain, oedema, sleep problems , mood problems) [Selectable (show checkbox)]
        - Local irritation [Selectable (show checkbox)]
    - Surgical treatment [Selectable (show checkbox)]
        - No adverse events [Selectable (show checkbox)]
        - Mortality rate [Selectable (show checkbox)]
          mention of mortality rate, regardless of number of deaths
        - Stroke [Selectable (show checkbox)]
        - CSF leak [Selectable (show checkbox)]
        - Meningitis [Selectable (show checkbox)]
        - Diplopia [Selectable (show checkbox)]
        - Corneal anaesthesia/keratitis [Selectable (show checkbox)]
        - Hearing/olfactory [Selectable (show checkbox)]
        - Numbness [Selectable (show checkbox)]
            - Barrow Neurological Institute Facial Numbness Scale [Selectable (show checkbox)]
            - Likert scale [Selectable (show checkbox)]
        - Sensory changes other than numbness CNV Paraesthesia/Dysaesthesia [Selectable (show checkbox)]
        - Anaesthesia dolorosa [Selectable (show checkbox)]
        - Masticatory weakness [Selectable (show checkbox)]
        - Facial nerve dysfunction [Selectable (show checkbox)]
            - House Brackman Scale [Selectable (show checkbox)]
        - Herpetic eruptions/herpes simplex [Selectable (show checkbox)]
        - Wound complications [Selectable (show checkbox)]
        - Landriel Ibanez classification [Selectable (show checkbox)]
    - Mixed treatments [Selectable (show checkbox)]
        - No adverse events [Selectable (show checkbox)]

- PARTICIPANT DISPOSITION [Selectable (show checkbox)]
    - Flow diagram - Not specific [Selectable (show checkbox)]
    - STROBE reporting [Selectable (show checkbox)]
    - CONSORT diagram [Selectable (show checkbox)]

APPENDIX 2 – Chapter 4

Search strategy for the systematic review

Search in Medline - Pubmed

Search number	Query	Filters	Results
10	#8 AND (english[Language])	Full text	**196**
9	#8 AND (english[Language])		203
8	#6 NOT #7		223
7	(“addresses”[Publication Type] OR “biography”[Publication Type] OR “case reports”[Publication Type] OR “comment”[Publication Type] OR “directory”[Publication Type] OR “editorial”[Publication Type] OR “festschrift”[Publication Type] OR “interview”[Publication Type] OR “lectures”[Publication Type] OR “legal cases”[Publication Type] OR “legislation”[Publication Type] OR “letter”[Publication Type] OR “news”[Publication Type] OR “newspaper article”[Publication Type] OR “patient education handout”[Publication Type] OR “popular works”[Publication Type] OR “congresses”[Publication Type] OR “consensus development conference”[Publication Type] OR “consensus development conference, nih”[Publication Type] OR “practice guideline”[Publication Type]) NOT (“animals”[MeSH Terms] NOT “humans”[MeSH Terms])		4,076,074
6	#3 AND #4 AND #5		234
5	((((((“patient reported outcome”[Title/Abstract]) OR (PROM[Title/Abstract])) OR (PROMS[Title/Abstract])) OR (“questionnaire*”[Title/Abstract])) OR (“patient reported outcome measure”[Title/Abstract])) OR (“tool”[Title/Abstract])) OR (“form”[Title/Abstract])		1,881,000
4	(instrumentation[sh] OR methods[sh] OR “Validation Studies”[pt] OR “Comparative Study”[pt] OR “psychometrics”[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR “outcome assessment (health care)”[MeSH] OR “outcome assessment”[tiab] OR “outcome measure*”[tw] OR “observer variation”[MeSH] OR “observer variation”[tiab] OR “Health Status Indicators”[Mesh] OR “reproducibility of results”[MeSH] OR reproducib*[tiab] OR “discriminant analysis”[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR “coefficient of variation”[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR “internal consistency”[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tw] OR precision[tw] OR imprecision[tw] OR “precise values”[tw] OR test-retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa’s[tiab] OR kappas[tiab] OR repeatab*[tw] OR ((replicab*[tw] OR repeated[tw]) AND (measure[tw] OR measures[tw] OR findings[tw] OR		9,198,335

	result[tw] OR results[tw] OR test[tw] OR tests[tw])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR “known group”[tiab] OR “factor analysis”[tiab] OR “factor analyses”[tiab] OR “factor structure”[tiab] OR “factor structures”[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab] AND scaling[tiab] AND (analysis[tiab] OR analyses[tiab])) OR “item discriminant”[tiab] OR “interscale correlation*”[tiab] OR error[tiab] OR errors[tiab] OR “individual variability”[tiab] OR “interval variability”[tiab] OR “rate variability”[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR “standard error of measurement”[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR (limit[tiab] AND detection[tiab]) OR “minimal detectable concentration”[tiab] OR interpretab*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR “meaningful change”[tiab] OR “ceiling effect”[tiab] OR “floor effect”[tiab] OR “Item response model”[tiab] OR IRT[tiab] OR Rasch[tiab] OR “Differential item functioning”[tiab] OR DIF[tiab] OR “computer adaptive testing”[tiab] OR “item bank”[tiab] OR “cross-cultural equivalence”[tiab])		
3	#1 OR #2		8,515
2	trigeminal neuralgia[Title/Abstract] OR trigeminus neuralgia[Title/Abstract] OR tic douloureux[Title/Abstract]		6,572
1	"trigeminal neuralgia"[MeSH Terms]		6,763

Search in Embase - OVID

1# (trigeminal neuralgia or trigeminus neuralgia or tic douloureux).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (10838)

2# exp trigeminus neuralgia/ (9840)

3# 1# or 2# (10838)

4# ("patient reported outcome" or PROM or PROMS or questionnaire or "patient reported outcome measure" or tool or form).ab. or ("patient reported outcome" or PROM or PROMS or questionnaire or "patient reported outcome measure" or tool or form).ti. (2261896)

5# (psychometr* or observer variation or reproducib* or reliab* or unreliab* or valid* or coefficient or homogeneity or homogeneous or internal consistency or cronbach* or correlation* or selection* or reduction* or agreement or precision or imprecision or precise values or test-retest or retest or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intra-observer or intertechnician or inter-technician or intratechnician or intra-technician or interexaminer or inter-examiner or intraexaminer or intra-examiner or interassay or inter-assay or intraassay or intra-assay or interindividual or inter-individual or intraindividual or intra-individual or interparticipant or inter-participant or intraparticipant or intra-participant or kappa* or repeatab* or replicab* or factor analysis or factor analyses or item discriminant or interscale correlation* or error or errors or individual variability or variability or standard error of measurement or sensitiv* or responsive* or ((minimal or minimally or clinical or clinically) and (important or significant or detectable) and (change or difference)) or (small* and (real or detectable) and (change or difference)) or meaningful change or ceiling effect or floor effect or Item response model or IRT).mp. or interpretab*.af. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (8775494)

6# 3# and 4# and 5# (277)

7# limit 6# to english language (254)

Search in PsychInfo

1# exp Trigeminal Neuralgia/ (436)

2# (trigeminal neuralgia or trigeminus neuralgia or tic douloureux).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (750)

3# 1 or 2 (750)

4# (psychometr* or observer variation or reproducib* or reliab* or unreliab* or valid* or coefficient or homogeneity or homogeneous or internal consistency or cronbach* or correlation* or selection* or reduction* or agreement or precision or imprecision or precise values or test-retest or retest or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intra-observer or intertechnician or inter-technician or intratechnician or intra-technician or interexaminer or inter-examiner or intraexaminer or intra-examiner or interassay or inter-assay or intraassay or intra-assay or interindividual or inter-individual or intraindividual or intra-individual or interparticipant or inter-participant or intraparticipant or intra-participant or kappa* or repeatab* or replicab* or factor analysis or factor analyses or item discriminant or interscale correlation* or error or errors or individual variability or variability or standard error of measurement or sensitiv* or responsive* or ((minimal or minimally or clinical or clinically) and (important or significant or detectable) and (change or difference)) or (small* and (real or detectable) and (change or difference)) or meaningful change or ceiling effect or floor effect or Item response model or IRT).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (1141972)

5# 3# and 4# (158)

6# limit 5# to (full text and english language) (60)

7# limit 6# to human (52)

Search in CINAHL

S1: TI (trigeminal neuralgia OR trigeminus neuralgia OR tic douloureux) OR AB (trigeminal neuralgia OR trigeminus neuralgia OR tic douloureux)

S2: TI (psychometr* or observer variation or reproducib* or reliab* or unreliab* or valid* or coefficient or homogeneity or homogeneous or internal consistency or cronbach* or correlation* or selection* or reduction* or agreement or precision or imprecision or precise values or test-retest or retest or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intra-observer or intertechnician or inter-technician or intratechnician or intra-technician or interexaminer or inter-examiner or intraexaminer or intra-examiner or interassay or inter-assay or intraassay or intra-assay or interindividual or inter-individual or intraindividual or intra-individual or interparticipant or inter-participant or intraparticipant or intra-participant or kappa* or repeatab* or replicab* or factor analysis or factor analyses or item discriminant or interscale correlation* or error or errors or individual variability or variability or standard error of measurement or sensitiv* or responsive* or ((minimal or minimally or clinical or clinically) and (important or significant or detectable) and (change or difference)) or (small* and (real or detectable) and (change or difference)) or meaningful change or ceiling effect or floor effect or Item response model or IRT)) OR AB (psychometr* or observer variation or reproducib* or reliab* or unreliab* or valid* or coefficient or homogeneity or homogeneous or internal consistency or cronbach* or correlation* or selection* or reduction* or agreement or precision or imprecision or precise values or test-retest or retest or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intra-observer or intertechnician or inter-technician or intratechnician or intra-technician or interexaminer or inter-examiner or intraexaminer or intra-examiner or interassay or inter-assay or intraassay or intra-assay or interindividual or inter-individual or intraindividual or intra-individual or interparticipant or inter-participant or intraparticipant or intra-participant or kappa* or repeatab* or replicab* or factor analysis or factor analyses or item discriminant or interscale correlation* or error or errors or individual variability or variability or standard error of measurement or sensitiv* or responsive* or ((minimal or minimally or clinical or clinically) and (important or significant or detectable) and (change or difference)) or (small* and (real or detectable) and (change or difference)) or meaningful change or ceiling effect or floor effect or Item response model or IRT))

S3: S1 AND S2

S4: S1 AND S2 Full Text

S5: S1 AND S2 ENGLISH

Search in HAPI

1 (trigeminal neuralgia or trigeminus neuralgia or tic douloureux).mp. [mp=title, acronym, descriptors, measure descriptors, sample descriptors, abstract, source] (17)

Risk of bias tables

Standards for evaluating the quality of PROM development		BPI-F			Penn FPS - R			QOL TN		
		Lee et al, 2010			Symonds et al, 2018			Luo et al, 2019		
a. PROM design										
General design requirements		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
1	Is a clear description provided of the construct to be measured?	A	A	A	A	A	A	A	A	A
2	Is the origin of the construct clear: was a theory, conceptual framework or disease model used or clear rationale provided to define the construct to be measured?	D	D	D	A	A	A	A	A	A
3	Is a clear description provided of the target population for which the PROM was developed?	A	V	V	V	V	V	A	A	A
4	Is a clear description provided of the context of use (i.e. discriminative, evaluative purpose, and/or predictive)	D	D	D	V	V	V	D	D	D
5	Was the PROM development study performed in a sample representing the target population for which the PROM was developed?	V	V	V	V	V	V	V	V	V
Concept elicitation (relevance and comprehensiveness)		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
6	Was an appropriate qualitative data collection method used to identify relevant items for a new PROM?	D	D	D	V	V	V	I	I	I
7	Were skilled group moderators/ interviewers used?	D	D	D	V	V	V	D	D	D

8	Were the group meetings or interviews based on an appropriate topic or interview guide?	D	D	D	A	V	V	D	D	D
9	Were the group meetings or interviews recorded and transcribed verbatim?	D	D	D	V	V	V	I	D	I
10	Was an appropriate approach used to analyse the data?	D	D	D	V	V	V	D	D	D
11	Was at least part of the data coded independently?	D	I	D	A	V		D	D	D
12	Was data collection continued until saturation was reached?	D	D	D	D	A	A	D	D	D
13	For quantitative studies: was the sample size appropriate?	D	D	D				D	D	D
	SUBTOTAL QUALITY CONCEPT ELICITATION STUDY *Lowest score of items 6-13*	**D**	**I**	**D**	**A**	**A**	**A**	**D**	**D**	**D**
	TOTAL QUALITY OF THE PROM DESIGN *Lowest score of items 1-13*	**D**	**I**	**D**	**A**	**A**	**A**	**D**	**D**	**D**
1b. Cognitive interview study or other pilot test										
		RATER 1	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
14	Was a cognitive interview study or other pilot test performed? *If NO skip items 15-35*	V	V	V	V	V	V	NO	NO	NO
General design requirements		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**

15	Was the cognitive interview study or other pilot test performed in a sample representing the target population?	A	A	A	V	V	V			
Comprehensibility		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
16	Were patients asked about the <u>comprehensibility</u> of the PROM? *If NO or not clear, skip items 17-25*	V	V	V	V	V	V	I	I	I
		RATER 1	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
17	Were all items tested in their final form?	V	V	V	V	V	V			
18	Was an appropriate qualitative method used to assess the <u>comprehensibility</u> of the PROM instructions, items, response options, and recall period?	D	A	D	V	V	V			
19	Was each item tested in an appropriate number of patients?	D	V	D	V	V	V			
20	Were skilled interviewers used?	D	D	D	V	V	V			
21	Were the interviews based on an appropriate interview guide?	D	D	D	V	V	V			
22	Were the interviews recorded and transcribed verbatim?	D	D	D	V	V	V			
23	Was an appropriate approach used to analyse the data?	D	D	D	V	V	V			
24	Were at least two researchers involved in the analysis?	D	D	D	V	V	V			
25	Were problems regarding the comprehensibility of the PROM instructions, items, response options, and recall	N	N	N	V	V	V			

	period appropriately addressed by adapting the PROM?										
	SUBTOTAL QUALITY OF COMPREHENSIBILITY STUDY *Lowest score of items 15-25*	**D**	**D**	**D**	**V**	**V**	**V**	**I**	**I**	**I**
Comprehensiveness		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
26	Were patients asked about the comprehensiveness of the PROM? *If NO or not clear, skip items 27-35*	NO	NO	NO	V	V	V	NO	NO	NO
		RATER 1	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
27	Was the final set of items tested?				A	A	A			
28	Was an appropriate method used for assessing the comprehensiveness of the PROM?				V	V	V			
29	Was each item tested in an appropriate number of patients?				V	V	V			
30	Were skilled interviewers used?				V	V	V			
31	Were the interviews based on an appropriate interview guide?				V	V	V			
32	Were the interviews recorded and transcribed verbatim?				A	V	V			
33	Was an appropriate approach used to analyse the data?				V	V	V			
34	Were at least two researchers involved in the analysis?				V	V	V			

35	Were problems regarding the comprehensiveness of the PROM appropriately addressed by adapting the PROM?					V	V	V				
	SUBTOTAL QUALITY OF COMPREHENSIVENESS STUDY *Lowest score of items 15, 26-35*		**D**	**I**	**D**	**A**	**A**	**A**				
		TOTAL QUALITY OF THE PILOT STUDY *Lowest score of items 14-35*	**D**	**D**	**D**	**A**	**A**	**A**	**I**	**I**	**I**	
		TOTAL QUALITY OF THE PROM DEVELOPMENT STUDY *Lowest score of items 1-35*	**D**	**I**	**D**	**A**	**A**	**A**	**I**	**I**	**I**	

Abbreviations: PROM=patient reported outcome measure, BPI-F=Brief Pain Inventory Facial, TN QOLS=Trigeminal Neuralgia Quality of Life Score, Penn FPS - R =Penn Facial Pain Scale Revised

Score: V= very good; A = adequate; D = doubtful; I = inadequate; N= not applicable

Standards for evaluating structural validity, internal consistency, responsiveness		**BPI - Facial**			**TNQOLS**		
		Lee et al, 2010			**Luo et al, 2019**		
Structural validity		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
	Unidimensionality or structural validity?						
1	For CTT: Was exploratory or confirmatory factor analysis performed?	A	A	A	V	V	V
2	For IRT/Rasch: does the chosen model fit to the research question?						
3	Was the sample size included in the analysis adequate?	A	A	A	D	D	D
4	Were there any other important flaws?	V	V	V	D	D	D
	TOTAL *Lowest score of items 1-4*	**A**	**A**	**A**	**D**	**D**	**D**
Internal consistency		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
1	Was an internal consistency statistic calculated for each unidimensional (sub)scale separately?	V	V	V	V	V	V
2	For continuous scores: Was Cronbach's alpha or omega calculated?	V	V	V	V	V	V
3	For dichotomous scores: Was Cronbach's alpha or KR-20 calculated?						
4	For IRT-based scores: Was standard error of the theta (SE (θ)) or reliability coefficient of estimated latent trait value (index of (subject or item) separation) calculated?						
5	Were there any other important flaws?						
	TOTAL *Lowest score of items 1-5*	**V**	**V**	**V**			
Responsiveness							
a. Criterion approach (i.e. comparison to a gold standard)		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**

1	For continuous scores: Were correlations between change scores, or the area under the Receiver Operator Curve (ROC) curve calculated?						
2	For dichotomous scales: Were sensitivity and specificity (changed versus not changed) determined?						
3	Were there any other important flaws?						
	TOTAL *Lowest score of items 1-3*						
b. Construct approach (i.e. hypotheses testing; comparison with other outcome measurement instruments)		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
4	Is it clear what the comparator instrument(s) measure(s)?				I	I	I
5	Were the measurement properties of the comparator instrument(s) adequate?				I	I	I
6	Was the statistical method appropriate for the hypotheses to be tested?				I	I	I
7	Were there any other important flaws?				I	I	I
	TOTAL *Lowest score of items 4-7*				**I**	**I**	**I**
c. Construct approach: (i.e. hypotheses testing: comparison between subgroups)		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
8	Was an adequate description provided of important characteristics of the subgroups?						
9	Was the statistical method appropriate for the hypotheses to be tested?						
10	Were there any other important flaws?						
	TOTAL *Lowest score of items 8-10*						

d. Construct approach: (i.e. hypotheses testing: before and after intervention)		**RATER 1**	**RATER 2**	**CONSENSUS**	**RATER 1**	**RATER 2**	**CONSENSUS**
11	Was an adequate description provided of the intervention given?				I	I	I
12	Was the statistical method appropriate for the hypotheses to be tested?				I	I	I
13	Were there any other important flaws?				I	I	I
	TOTAL *Lowest score of items 11-13*				**I**	**I**	**I**

Abbreviations: PROM=patient reported outcome measure, BPI-Facial=Brief Pain Inventory Facial, TN QOLS=Trigeminal Neuralgia Quality of Life Score

Score: V= very good; A = adequate; D = doubtful; I = inadequate; N= not applicable

APPENDIX 3 – Chapter 5

Consent form – Focus group

TRINCOS: IRAS ID 240304 Sponsor Ref: B1262 F10153319 V 1.1 14 May 2020

Centre Number:

Study Number:

Participant Identification Number for this trial:

Title of Project: TRINCOS – DEFINING THE CORE OUTCOME SET FOR TRIGEMINAL NEURALGIA

Name of Researcher: Carolina Venda Nova

Please initial box:

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have these answered to my satisfaction. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. This will not affect my medical care or legal rights. ☐

3. I agree that relevant sections of my medical notes may be looked at by researchers, responsible individuals from regulatory authorities where it is relevant to my taking part in research, the sponsor University College London (UCL), and NHS Trust. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me might be used to support other research in the future and may be shared anonymously with other researchers. ☐

5. I agree to be contacted by letter/phone/email in case researchers need to clarify some information about my health. ☐

6. I agree that researchers use the data already collected for research even though I withdraw from the study. ☐

7. I agree to participate in the FACE TO FACE focus group discussion during which I will be asked to indicate the outcomes that are important to me in the treatment of Trigeminal Neuralgia. I am aware that the discussion will be audio recorded. ☐

8. I agree to participate in the ONLINE focus group discussion during which I will be asked to indicate the outcomes that are important to me in the treatment of Trigeminal Neuralgia. I am aware that the discussion will be audio and video recorded. ☐

9. I agree to participate on a consensus meeting, with other patients and with doctors. ☐

10. I agree to my General Medical Practitioner (GP) being informed of my participation in the study. ☐

11. I agree to being contacted about other trigeminal neuralgia studies. ☐

12. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Participant Information Sheet (PIS)

We would like to invite you to participate in our research project

Title: Defining Core Outcome Sets in Trigeminal Neuralgia – The TRINCOS Study

Contents

Investigators:

- Professor Joanna M Zakrzewska, University College London
- Professor Sarah Baker, Sheffield Dental Hospital
- Dr Richeal Ni Riordain, University College London
- Carolina Venda Nova (PhD student), University College London

Please read this sheet carefully. Please ask if you do not understand or would like more information.

You are being invited to take part in a research study. This is a post graduate student research project. Before you decide, it is important for you to understand why the research is being done and what will happen. Please take time to read the following information carefully.

1. **What is the purpose of this study?**

   In medicine we aim to treat patients with medications or procedures that will be most effective with the fewest possible side effects. To achieve this goal, we must consider the research that has been done, the desires of the patients and our clinical experience. It would be ideal, when at the available treatment options for trigeminal neuralgia (TN), to be able to compare one research study with the next. This is rarely possible as the outcomes measuring the merits of medications or procedures are rarely the same. The aim of this study is to ask patients and clinicians which outcomes should be used as a standard set in all TN research. Using this standard set should ensure we can gather the most worthwhile information which is important to patients, doctors and researchers. These can then be used as standard in research and clinics.

2. **Why am I being asked to take part?**

   You have been identified as potential participant by doctors in your clinic because you have been diagnosed with Trigeminal Neuralgia.

3. **Do I have to take part?**

   No, it is up to you to decide whether or not to join the study. If you are interested, we will go through this information sheet with you and answer any questions you may have. You can take as much time as you need to decide if you would like to participate in the study or not. Even if you agree to take part in the study you are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive in this hospital. Participation in this study will in no way affect your legal rights.

4. What do I have to do to enroll in the study?

Potential participants will be identified in routine clinics or through the Trigeminal Neuralgia Association UK (TNAUK) , patient support group. As you have agreed we are providing you with this Patient Information Sheet (PIS). You will be given adequate time to decide whether to participate further in the study. The inclusion criteria are as follows:

- A diagnosis of Trigeminal Neuralgia not due to a tumour
- Willingness to participate in group discussion face to face or online
- If you accept to participate on the online focus group meeting, you will have to have access to:
    - Strong internet bandwidth,
    - Computer or mobile phone with a camera and a microphone

If you decide you would like to participate in the study, you can tell us at the time of your appointment. If you have seen the study advertised on TNA UK, you can **contact us by e-mail (carolina.venda-nova@nhs.net)**. We will book an appointment for you to participate in **one group discussion, called a focus group.** This group discussion might be face to face, in a quiet room, or online, using a software that allows a group of people to interact without having to be physically in one room.

We have added the option of running the discussion online, in view of the current pandemic with COVID19.

Other patients who have Trigeminal Neuralgia, will also participate. The group discussion will last **up to 90 minutes**. You will be asked to sign a consent form, which will provide you with information on the study and what data we will be collecting. Once the consent form has been signed, we will conduct the group discussion.

5. What will happen to me if I take part?

a. A total of up to 32 individuals with Trigeminal Neuralgia will participate in this part of the study. You will be invited to join a small group of patients (maximum 8) for the discussion. The groups will either gather in a conference room at the Eastman Dental Hospital, London, or an online meeting will be set up and you can be in the comfort of your home, while participating. If you opt for the online discussion, you will be sent instructions on how to join. A facilitator will lead the group discussion, asking you to discuss what outcomes are important to you in treating your TN. **The discussion may last up to 90 minutes**, after this, you are free to go home or you can just disconnect from the computer program if you are at home, using your computer.

b. If you opt for the online focus group, two members of the team will be online to guide the patients with any technical issues, so you will be supported throughout the meeting.

c. Once we have completed all the focus groups, we would like to **ask you to attend <u>one</u> consensus meeting.** Other patients and some doctors will also be present. In this meeting we will finalize the results.

6. <u>What are the possible risks/side effects of taking part?</u>

We do not foresee any risks in participating in this study. There is no intervention in this study and therefore no side effects are expected.

7. <u>What are the possible benefits of taking part?</u>

We hope to learn what treatment outcomes are important to you about the management of your Trigeminal Neuralgia. Developing this list of outcomes will allow comparisons between different treatment types. This will help everyone to determine which is the best treatment for each patient with TN. We will also be asking the experts (clinicians and researchers) about what they consider the main outcomes should be. You will have the opportunity of hearing their point of view at the consensus meeting.

8. <u>What if there is a problem?</u>

Any complaint about the way you have been dealt with during the study will be addressed. The detailed information concerning this is given in the next part of this information sheet. If you have any concerns or complaints, you should contact your study doctor in the first instance.
University College London (UCL) holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions.

If you remain unhappy, you can make a formal complaint through the National Health Service (NHS) complaints procedure. Details can be obtained through the University College London Hospitals (UCLH) Patient Advice and Liaison Service (PALS) on 0207 3447 3041, email: <u>PALS@uclh.nhs.uk</u>, address: PALS, Ground Floor Atrium, University College Hospital, and 235 Euston Road, London, NW1 2BU.

9. Confidentiality – who will have access to the data and findings?

All study participants will be identified by a study number and not by their personal data. Only the above team will be able to match your study number to your medical records. This list will be kept on a secure NHS password protected site. When the focus group starts, the discussions will be audio recorded. If you participate on the online focus group, the discussion will be video and audio recorded but only the audio file will be sent for transcribing. The recording will be transcribed within 48 hours and the information from the group discussion will be reviewed.

Once the audio records are transcribed, they will be destroyed. The typing of the group discussion will be anonymized. We will store the transcript in a locked filing cabinet in a secure magnetic card accessed building. As backup a second copy will be kept on a password-protected computer. Only researchers associated with the study will have access to the transcript.

Individuals from UCLH and regulatory organisations may look at your medical and research records to check the accuracy of the research study.

You can find out more about how we use your information by contacting Deborah Dillon: deborah.dillon2@nhs.net.

You will not be able to be identified through any of the data and information released from this study.

All patient information will be treated in the strictest confidence, in accordance with the Data Protection Act 1998. UCLH will keep non-identifiable information about you from this study for 10 years after the study has finished. If you withdraw from the study, we will keep the information about you that we have already obtained.

If you have any questions about this study, please talk to:

Name: Carolina Venda Nova

Telephone:

Address **:** Royal National ENT & Eastman Dental Hospitals 4th Floor Central, 250 Euston Rd, NW12PQ

10. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available. If this happens, we will tell you about it and discuss whether you want to continue in the study. If you decide to continue you will be asked to sign an updated consent form.

11. What happens if I decide to withdraw from the study?

This will not affect your medical care in any way.

12. Will my GP be informed?

With your consent we would like to inform your GP of your participation in this study by sending them a letter.

13. What happens when the research study stops?

After we have performed our analysis, we can provide you with the results and explain what it means, if you wish so. You will need to continue the regular visits to the Oral Medicine/Facial Pain Department at the Eastman Dental Hospital, or Sheffield Dental Schools.

14. What will happen to the study results?

We will use the results to present at conferences and prepare publications in medical/scientific journals. We will publish details of the research in the TNAUK newsletter and on their website and present the results at their meetings. We hope that this will help in the management of Trigeminal Neuralgia. **No details that specifically identify you will be included**. We can provide you with details of any publication, at your request**.**

15. Who is organizing and funding the research?

This study has been designed and organized by senior staff members of the Eastman Dental Institute. We have funding from The Rosetrees Trust and from the TNAUK.

16. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favorable opinion by The North of Scotland Research Ethics Committee (1). It has also been reviewed by the Rosetrees Trust.

17. More information about taking part

I. Expenses and payments

You will receive a payment of £30 for your participation in the group discussion whether online or face to face. You will also be able to claim the costs of public transport to and from the group discussion to a maximum of £15.

18. Contact details for further information:

You are encouraged to ask any questions you wish, before, during or after your participation in this study.

Name **:** Carolina Venda Nova

Tell :

e-mail **:**

Address **:** Royal National ENT & Eastman Dental Hospitals 4th Floor Central, 250 Euston Rd, NW12PQ

Name **:** Professor Joanna M Zakrzewska

e-mail **:**

Address **:** Royal National ENT & Eastman Dental Hospitals 4th Floor Central, 250 Euston Rd, NW12PQ

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

Focus group guide

Moderator Introduction and Purpose of Group (2 minutes)

Hello. My name is CVN, and I am a PhD student. Also present on this meeting is (…). I would like to start off by thanking each of you for taking time to participate today. We'll be here for about 90 minutes. The reason why we are here today is to gather your opinions about what the treatment outcomes for trigeminal neuralgia should be. I'm going to lead our discussion today. I will be asking you questions and then encouraging and moderating our discussion.

I would like you to know that this focus group will be audio recorded. The audio recording, which will be transcribed later this week to allow us to analyse the data.
The identities of all participants will remain confidential. The recording allows us to revisit our discussion to ensure we have interpreted your comments correctly and the results can then be used for developing research papers and presentations.

Ground rules (3 minutes)

To allow our conversation to flow more freely, I'd like to go over some ground rules.

1. Only one person speaks at a time. This is doubly important as our goal is to make a written transcript of our conversation today. It is difficult to capture everyone's experience and perspective on our audio recording if there are multiple voices at once
2. Everyone doesn't have to answer every single question, but I'd like to hear from each of you today as the discussion progresses.
3. This is a confidential discussion in that I will not report your names or who said what to anyone. Names of participants will not even be included in the final report about this meeting. It also means, except for the report that will be written, what is said in this room stays in this room.
4. We stress confidentiality because we want an open discussion. We want all of you to feel free to comment on each other's remarks without fear your comments will be repeated later and possibly taken out of context.
5. There are no "wrong answers," just different opinions. Say what is true for you, even if you're the only one who feels that way. Don't let the group sway you. But if you do change your mind, let us know.
6. We will have a break midway, for about 10 minutes.
7. Are there any questions?

Icebreaker question (3min)

Before we start, if you could travel anywhere in the world right now (without any money, or COVID restrictions), where would you go and why?
I'll start…..

Focus Group Questions (80 minutes)

1.1. Knowledge about TN (5 min)

1.1.1. What do you understand about you condition? If you had to explain TN to a friend or a relative what would you say?

1.2. Experience of living with TN (10 min)

1.2.1. How would you describe the impact TN has had on your personal and professional life?

Prompts: Quality of life – activity limitations – Have you had problems while eating, chewing, touching, brushing, kissing?

Mood: have you stopped doing things due to the emotional burden of TN? Have you worried? Do you think that your mood has any influence on your pain?

Family and social interactions – has anything changed with regards to intimacy? Have you stopped making plans with your friends or family? Have you stopped going out for meals?

Productivity – have you stopped working due to TN? Have you had to take time off work?

2. Think about the time when you were given a treatment (it does not matter if it was a tablet or surgery or pain management psychology):

2.1.1. Would you say that it was successful? If not, how would you describe a successful treatment? (10 min)

2.1.2. How important are the side effects/complications of treatment to you? (5min)

2.1.3. When you think about your treatment (s), how important is it to you that the treatment has an impact on your mood? (5min)

3. I would like you to think about a time when you were in pain:

3.1.1. What would an ideal treatment do for you at that time? (15 min)

Prompts: would the ideal treatment reduce pain intensity, reduce number of attacks, reduce frequency of attacks, provide immediate pain relief, reduce anxiety, have few side effects that would allow for your tasks work to continue)

3.1.2 How important would be to you that a treatment could change the number and frequency of TN attacks you have? (5 min)

4. I would like you to think about a time/period when you were pain free/in remission

4.1.1. How would you describe this period? (5 min)

4.1.2. What would an ideal treatment do for you at this time? (5 min)

Prompts: Is reduction of fear of pain return and important outcome? Anxiety or catastrophizing about a new attack?

5. Today we have talked about a lot of outcomes that are important when deciding on a treatment.
   5.1. If you had to think about a list of the most important treatment outcomes (maybe 3 or 4), what would they be? (10 min)

6. Is there anything else that you think is important for us to hear about your experience of living with TN that we have not covered today? (5min)

Closing (2 minutes)

Thanks for your participation today. Your comments have given us lots of valuable information. We thank you for your time.

Example of notes taking and coding extract

Transcript	Notes and ideas	Coding
FGA4: I think it's being pain free definitely, that's the main thing because that's the main thing that affects everything isn't it really, is having that pain and if you haven't got the pain obviously you can just carry on your life as normal. So I think the pain side of it is for me the most important, definitely.	Meaning of normal= Pain free=normal life Pain most important aspect of disease	Pain outcomes
I: You're both nodding – are you in agreement?		
FGA2: Yeah, I would say ideally success would be pain free, off the medication, it's all gone but the reality is to a certain extent for me if and when I get an attack it's making sure that you have the balance of the medication right and that can then take a period of time before it helps it to calm down. So even though I'm still taking the medication now even speaking I can feel like there's a slight dull ache but I think I've reached the point where I can accept it's there and I don't want to take any more medication but if it	Success of treatment=pain free treatment Vigilant coping strategy	Pain outcomes Cognitive adaptation Coping

then starts getting worse then I will increase it. So ideal pain free but if you can take medication which will help control and reduce the pain that would be great.	There is a shift into adapting to a condition – self regulatory model (Leventhal)	Cognitive adaptation
FGA4: I think you don't realise how much pain you're in when you have that dull ache all the time, you just get used to having that dull ache. It's there. I live with that. I just don't want to take more medication to get rid of that dull ache. So it would be ideal if it just went away but it doesn't. I just feel that I don't want to take more to get rid of that dull ache. I can cope with that. It's just those attacks where you can't do anything, it sets it off. Just having this dull ache all the time, whether that makes the pain increase or if I made that dull ache go away does it make the pain recede or if I keep that dull ache and just get on with it. I don't know. I don't know what's the best thing sometimes. Whether to take more medication and get rid of that dull ache. Does it make any difference to the dull ache, does it increase or does it just stay there?	This is a lovely description/summary of the points about the weighing up of pain, medication and the decisions that have to be made about coping. They are always vigilant.	Pain outcomes Cognitive processing Hypervigilance Coping

Additional quotes illustrative of themes and sub-themes

Themes	Sub-themes	Participant quotes
Characteristics of Trigeminal Neuralgia	Descriptors of TN	*FGC1: "A total stabbing pain."* *FGB2": "Mine was absolutely constant, all the time, excruciating pain."*
	Uncertainty about aetiology	*FGB1: "My understanding is that there is some issue with the trigeminal nerve, the myelin sheath, that is just random and uncontrollable I suppose, that's the thing you don't know when or why. There could be compression, there may not be some compression. It is just variable really."*
	Prognosis – How chronic is chronic TN pain?	*FGA2: "... from what I have read, it says it could gradually get worse as you gradually get older, I don't know how true that actually is."*
Impact of living with Trigeminal Neuralgia		*FGC4: "It made me very depressed, to be honest with you. I had to go onto tablets for anxiety and things like that and I just went into a hole, if you know what I mean. So they had to keep upping my medication. It wasn't good."*

Themes	Sub-themes	Participant quotes
	Psychological impact	*FGB5: "I agree about mood. It's difficult to quantify it all and I think you just adapt your life, as you say. You don't want to feel sorry for yourself, X said there's other people with things far worse but it can overwhelm you sometimes."* *FGA1: "What medication are you on?" FGA3: "No, I have stopped mine now, that is what I was saying. I stopped it in October and then I took it again for a few months... and now I am of it again but I do think you get to that pain threshold where you just kind of have to go to get to the point where you try not to feel it all the time because it is so depressing."* *FGC1:"I have had three different tablets and now it is in remission at the moment but I feel I can't stop the tablets because I really don't want it back again."*
	Functional impact and daily life activities	*FGB3: "I used to find, just normal things, like going out for a meal, going for a run, doing all the things that you might like doing, if you are having a bad time with it, it affects absolutely everything."*
		FGB5: "I had a particularly bad episode earlier this year where I had to stop working. I am a teacher. Because I couldn't talk at all when an attack came on."

Themes	Sub-themes	Participant quotes
	Social impact	*FGB2: "in terms of impact on work (…) so I facilitate teaching and I do coaching in leadership development so when the pains were coming up it was like I literally cannot talk (…) I reached the point where I needed to say to my clients – I am sorry, this could come up at any moment, I can't commit to do this with you – and then began to pull out of a few things."* *FGB3: "I had episodes where it does affect your social relationships where one person who in a way, I'm not so close to now said - Where did you disappear to? -, I said well, I don't think I disappeared, I was ill but that didn't quite land. So it does affect your social relationships in one way or another because you're just not there as much."* *FGA3: "And even if you decide that you're going to try to do something like someone's birthday (…) my husband would say oh, shall we go to John's birthday and I'd think oh God, really? (…) I'm not touching or kissing or whatever, and then it's like you put something into your mouth, whether it's a piece of cake or something so you look like this slightly miserable person as well. So you don't want to be that miserable person and you don't want to make the other people in the crowd miserable either so you kind of think oh, I just stay home, you go."* *I: "Does it stop you doing things with the family then?" FGA3: "Yeah. I think so. It doesn't stop you because after a while you just accept that's the way it is but initially, you are kind of like how do you*

Themes	Sub-themes	Participant quotes
		explain it to someone because if you say to somebody, I've got this really bad pain they kind of think you've got toothache and then nobody really except all of us understand that that pain is just breath-taking." *FGC2: "Basically it was really hard to eat until we started treatment but life was impossible for me, I couldn't play with the kids, I couldn't go to any of the things I used to do. It really messed my life."* *FGB2: "And it's just hard to explain to people, isn't it? Most people haven't really heard about it and they can't really see anything, and as we know, it's excruciating."*
	Cognitive processes	*FGB3: "When you are pain free, in the back of your mind all the time, I find in my mind all the time that oh my goodness, if that comes back what will I do. So yeah, it has quite an impact on your life. It's only now talking about it you realise all these years you just find ways of coping."* *FGB2: "As debilitating as it is I think in some respects I just try to put things into perspective. I guess there are a lot of people worse off in the world. I know it's very painful and it can be… inconvenient is the wrong word but it can be debilitating certainly, there are some kinds of treatments to kind of deal with what we've got but you get come people that get to a position where they can't be helped, so for that I am grateful."*

Themes	Sub-themes	Participant quotes
Navigating through treatment outcomes	The meaning of a successful treatment – *"I'd like to get rid of it* (PAIN) *completely."*	*FGB1: "They are almost asking us to compromise in terms of saying, we don't want to be pain free, we just want to be pain free 50% of the time. No, we want to be pain free. There might be other things that we will put up with as everybody has been saying but pain free has got to be the ultimate objective."*
	Negotiating side effects	*FGC4:"I did get side effects from a couple of tablets and I have settled on one now. I don't want to stop taking it but I was warned that having an operation could leave my face numb and I really worried about that so persevered basically with the pain until the tablets seem to have controlled it. And I don't know whether it will come back or not but I think it would be really a last resort for me* (surgery)*."*
	Supported self-management	*FGA4:" I think we would all like to be pain free, we would all like that silver bullet, but we know that at the moment is not there so what else can help us is, well, I have said it, talking therapy I think would really help."*
	The intricacies of normality	*FGB1: "We will take whatever is available which will allow us to have as normal an existence as possible but ultimately I want a treatment or a medication which is going to stop it."*
		FGC2: "It's really good to have kind of a direct line when you need to ask or you need support or anything, I think it's a good idea, it can make the difference."

Themes	Sub-themes	Participant quotes
Health care access, awareness, and peer support	Streamlined access to health care	*FGC5: "If there was some form of clinic that you could use and ring up and speak to somebody it would be really helpful."*
	Health care professionals' awareness	*FGB5: "So when you meet Dr Y, (…) and they can empathise it just does feel very, very supported. I had an experience with a GP who was also, I couldn't believe it because normally it feels like nobody really understands or was that bothered but one GP, he just said gosh, you're doing really well, that must be really hard. Just that little bit of empathy, I think we probably alluded to it, just that somebody can understand a little bit that you're trying your hardest and it's really difficult."*
	Peer support	*FGA1:" I am sure some sort of support group wouldn't be a bad idea." A telephone line. I don't know if a telephone line would work in the same way. You need to have groups, don't you?"* *FGA4:" I think it is nice to see who you are talking to and relate to them, I think you would relate to them more if you can actually see who they are than just make a phone call."*

APPENDIX 4 – Chapter 6

Delphi survey – email to participants

Email sent to prospective participants (clinicians, researchers, members of the industry):

"Dear,

We would like to invite you to participate in our research project. We are conducting a Delphi study – this is an anonymized online survey – to gain the views of patients or their representatives, clinicians and researchers, about what they consider to be the important treatment outcomes for Trigeminal Neuralgia.

You might be aware of the difficulties in combining study results in the field of Trigeminal Neuralgia due to utilisation of multiple outcomes and outcome measures which have not been standardised. Most studies collect data on pain levels, yet the burden of Trigeminal Neuralgia is significant, not only on daily life but also on mood.

This online survey consists of 3 rounds, 4 weeks apart. Each round should not take longer than 15-20 minutes to complete. You can find more details about the project on the attached information leaflet.

Please follow this link to the registration page and to the first round of our online survey:

https://delphimanager.liv.ac.uk/TRINCOSDELPHI/

Please forward this email to any colleagues (clinicians, researchers or members of industry) that you think could contribute to this survey.

We would like to thank you in advance for your support with our research project.

Best wishes,"

Email sent to patients:

“Dear,

Thank you so much for your email and for wanting to participate in our research.

I am recruiting patients for the following task:

Online survey – this will likely start at the beginning of March, there will be 3 surveys, 4 weeks apart. In this survey, we ask patients to vote on what they think the most important outcomes for the treatment of TN are. Each survey should not take longer than 15 minutes to complete. The survey is anonymous. Even though you write your name and address on the first page, this will only be visible to me, as I am in charge of the programme.

Attached you can find more information about the online survey.

I cannot thank you enough for your availability.

Please feel free to contact me at any time if you have any further questions.

Best wishes, “

Delphi survey - participant information sheet (PIS)

We would like to invite you to participate in our research project

Title: Defining Core Outcome Sets in Trigeminal Neuralgia – The TRINCOS Study

Investigators

• Principal Investigator - Professor Joanna M Zakrzewska, University College London j.zakrzewska@ucl.ac.uk

• Carolina Venda Nova (PhD student), University College London, carolina.nova.18@ucl.ac.uk

• Professor Sarah Baker, Sheffield Dental Hospital

• Dr Richeal Ni Riordain, University College London

Please read this sheet carefully.

You are being invited to take part in in a Delphi study – this is an anonymized online survey. Before you decide whether or not you would like to take part, it is important for you to consider why the research is being done and what it will involve. Please read this information sheet carefully.

1. What is the purpose of this study?

The primary objective of the TRINCOS study is to determine the core treatment outcomes (core outcome set, COS) for Trigeminal Neuralgia (TN). We propose that a COS needs to be developed to ensure that trials report useful outcomes, which benefit patients, clinicians and healthcare service providers alike.

2. Why am I being asked to take part?

You are being invited to take part as you have been identified as:

1. Patient with Trigeminal Neuralgia

We are keen to gain your views about what you consider to be the important treatment outcomes for Trigeminal Neuralgia.

3. What will I be asked to do if I take part?

You will be asked to participate in a Delphi survey consisting of three rounds:

Round one: This will involve completing an online survey rating the treatment outcomes for trigeminal neuralgia on how important you think they are. This should take no longer than 15 minutes.

Round two: You would subsequently receive a summary of the group's response and a further online questionnaire to re score each outcome for importance in light of the 'whole group' scores. This should take no longer than 15 minutes.

Round three: Similar to round two, but you will also be asked to indicate which outcomes you think should form part of the final core outcome set for TN. This should take no longer than 15 minutes.

4. Who is organizing and funding the research?

This study has been designed and organized by the TRINCOS research team members from the Eastman Dental Institute and Sheffield Dental School. We have funding from The Rosetrees Trust and from the TNAUK.

The Delphi rounds will be organized by Dr Carolina Venda Nova, UCL PhD student, and supervised by Professor Joanna Zakrzewska, Professor Sarah Baker and Dr Richeal Ni Riordain.

5. Confidentiality – who will have access to the data and findings?

All study participants will be identified by a study number and not by their personal data.

You will not be able to be identified through any of the data or information released from this study.

All patient information will be treated in the strictest confidence, in accordance with the Data Protection Act 1998.

If you have any questions about this study, please talk to: Carolina Venda Nova, carolina.nova.18@ucl.ac.uk

6. What will happen to the study results?

We will use the results to present at conferences and prepare publications in medical/scientific journals. We will publish details of the research in the TNAUK newsletter and on their website

and present the results at their meetings. We hope that this will help in the management of Trigeminal Neuralgia. **No details that specifically identify you will be included**. We can provide you with details of any publication, at your request**.**

7. Data protection

Anonymized survey responses will be collected using the DelphiManager platform. Results will be downloaded to an encrypted University College London computer to allow analysis by the research team. Data will be stored for the duration of the research project only and then deleted. You have the right to access submitted information according to UK data protection laws.

Local Data Protection Privacy Notice

Notice:

The controller for this project will be University College London (UCL). The UCL Data Protection Officer provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk

This 'local' privacy notice sets out the information that applies to this particular study. Further information on how UCL uses participant information can be found in our 'general' privacy notice:

For participants in health and care research studies, click here

The information that is required to be provided to participants under data protection legislation (GDPR and DPA 2018) is provided across both the 'local' and 'general' privacy notices.
The lawful basis that will be used to process your personal data are: 'Public task' for personal data.

Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk.

8. Who has reviewed the study?

This study has been reviewed and given favorable opinion by University College London. It has also been reviewed by the Rosetrees Trust.

9. Contact details for further information:

You are encouraged to ask any questions you wish, before, during or after your participation in this study.

Name : Carolina Venda Nova
e-mail : carolina.nova.18@ucl.ac.uk

Name : Professor Joanna M Zakrzewska
e-mail : j.zakrzewska@ucl.ac.uk

Thank you for taking the time to read this information sheet and to consider this study.

Delphi survey – final list of domains and outcomes to present in the first round

Domain	Outcome	Help Text
PAIN	Pain relief	Pain relief means that the pain reduces or is alleviated
PAIN	Pain intensity	Intensity of the pain or how much it hurts
PAIN	Pain free on medication	The treatment (medication or surgery) alleviates the pain completely, but patients need to be on medication long-term
PAIN	Pain free off medication	The treatment (medication or surgery) alleviates the pain completely without the need of long-term medication
PAIN	Quality of the pain – electric shock like	Intermittent shooting, sharp or electric shock like type pain
PAIN	Quality of the pain – constant burning	Constant burning or aching type pain
PAIN	Temporal aspects of pain	Frequency and number of TN attacks over time
PAIN	Pain interference	How much does TN causes interference on one's daily life
PAIN	Reduction in the need for rescue medication	Reduce the use of extra medication during an attack
PAIN	Trigger sensitivity	Pain triggers (touching the face, a light breeze, eating or the wind)
EMOTIONAL IMPACT	Depression	How important it is to check whether TN is causing or having an impact on mood: depression refers to negative mood, loss of self-confidence, loss of motivation and enjoyment
EMOTIONAL IMPACT	Anxiety	How important it is to check whether TN is causing or having an impact on mood: anxiety refers to worry, feeling fearful or restless

Domain	Outcome	Help Text
COGNITIVE IMPACT	Fear of pain or fear of an attack	How important it is to check whether fear of a TN attack is present even when the pain is controlled by treatment
COGNITIVE IMPACT	Coping	Coping mechanisms – ability to deal with stressful or difficult problems
COGNITIVE IMPACT	Catastrophising	Checking whether TN can have an impact on one's thoughts - people are said to be catastrophising when they think that the worst will happen
COGNITIVE IMPACT	Illness Beliefs	Beliefs and feelings about TN (for example cause, consequences, symptoms)
COGNITIVE IMPACT	Self-efficacy	Confidence and trust in the ability to deal with TN
COGNITIVE IMPACT	Self-Efficacy to Manage Emotions	Confidence to manage feelings of anxiety, depression, disappointment, or anger.
COGNITIVE IMPACT	Self-Efficacy for Managing Chronic Conditions	Confidence in managing tablets and dosages in challenging situations such as when travelling, when running low on medication or when side effects appear
PHYSICAL IMPACT	Self-care	Ability to look after oneself (washing, grooming, combing hair, brushing teeth etc)
PHYSICAL IMPACT	Eating	Ability to eat comfortably or at all
PHYSICAL IMPACT	Talking	Ability to talk
PHYSICAL IMPACT	Intimacy	Ability to be intimate with partners/spouses
SOCIAL IMPACT	Work ability	Ability to perform normal work-related activities
SOCIAL IMPACT	Ability to Participate in Social Roles and Activities	Ability to perform usual social roles and activities (meeting friends, leisure activities, etc)
SOCIAL IMPACT	Avoidance behaviour	Patients might anticipate or avoid an unpleasant or painful situation (for example,

Domain	Outcome	Help Text
		avoidance of certain foods, activities, social interactions, etc).
SOCIAL IMPACT	Social Validation	How important is it that family, friends, and colleagues understand TN
SOCIAL IMPACT	Social withdrawal and isolation	How important is it that patients withdraw from activities and isolate themselves due to TN
SOCIAL IMPACT	Peer support	How important is it that TN patients speak to other patients and support each other
SOCIAL IMPACT	Effect of TN on family or friends	How important is it that TN has an impact on family, carers, and friends
QUALITY OF LIFE	Health related QOL	How important is an individual's perceived well-being in physical, mental, and social aspects of health
GLOBAL IMPROVEMENT	Overall response to treatment	How important is it that patients feel better or worse on the whole following treatment, when compared to before treatment
SATISFACTION	Satisfaction with treatment	How important is it that patients are satisfied with their treatment
SIDE EFFECTS OF TREATMENT	Side effects of medication	How important are the side effects of medication
SIDE EFFECTS OF TREATMENT	Side effects of surgery	How important are the side effects of surgery
HEALTH CARE ACCESS	Literacy of GPs and dentists about TN	How important is it the level of doctors or dentist's knowledge about TN (symptoms, treatments, etc)
HEALTH CARE ACCESS	Access to a specialist TN clinic	How important it is to have access to a specialist TN clinic and ongoing health care support
HEALTH CARE ACCESS	Patient's literacy about Trigeminal Neuralgia	How important is it that patients have a good understanding of trigeminal neuralgia: causes, prognosis, investigations, and treatment options

Delphi survey – outcomes suggested by participants following first round

Outcome	Score 1-9
Frequency of paroxysms	9
Percentage of the day with concomitant background pain	7
Literacy of all healthcare professionals; including Care Home and A&E staff; about TN	8
Early Diagnosis (like many others I had not heard of TN)	9
The ability to access simple; written information on TN - preferably in digestible portions	8
The ability to speak to fellow sufferers who are knowledgeable about TN (eg; trained TNA UK volunteers)	8
Medics to truly listen when taking a medical history and not be dismissive to anything which they might consider irrelevant	8
Better communication between GPs and dentists	6
Better training of GPs; dentists and especially staff in A&E departments	9
Someone medically trained on call to answer questions about medication dosages	6
GPs to understand the debilitating side effects of anti-epileptic medication	6
Medics to be sympathetic about the fear aspect of newly diagnosed TN patients	6
Action to be taken against the misinformation on many social media sites; especially Facebook groups	7
Duration of pain relief	7
Support for patients in telling other professionals about TN as often not believed or minimised. Causes stress and avoidance in seeking help and medical needs.	6
Use of health care resources	5
Access to specialist care in a timely fashion with/immediately after a relapse or severe episode for urgent treatment i.e.first aid (? lidocaine injection? immediate commencement of new medication	7
Complications to neurosurgery	8
Understanding temporal limitations of different surgeries	7
Time to return to work/family responsibilities after surgery	8

Prevention of Anaesthesia Dolorosa (deafferentation pain)	9
Clearly; pain freedom off medication is the main outcome from management of TN.	8
Acceptability of trade-off between treatment efficacy and side-effects/complications	9
Feeling able to manage the pain (not just coping with pain)	9
Awareness of potential adverse drug interactions in patients taking medication for other conditions	6
Access to specialist psychology to learn coping strategies	9
Access to specialist nurse/clinician to help managing medications in the long term	7
Drs Understanding of TN in A &E	9
Information/literature on different types of medication that can be prescribed for TN and main & long term side effects of each.	9

Consensus meeting – information package

1. Email sent to participants

"Dear ,

Thank you once more for agreeing to participate in our study. There are important documents attached to this email.

Why are we doing this study?
The aim of our study is to define the Core Outcome Set (COS) for Trigeminal Neuralgia, i.e., the group of outcomes that should be used as a minimum in all future TN studies to improve the way we compare the results. This will help patients and doctors to decide what the best treatments are. We also need this COS to be easy to use, so there cannot be a high number of outcomes in the COS. Please see this video which explains what a COS is:

https://www.youtube.com/watch?v=g1MZi2mzK1U

Previous work:
We run a survey last year with patients, clinicians and researchers. Of the 40 outcomes presented, 17 were considered important, but there were 23 which did not reach consensus. We want to put these up for voting again - the list of 23 outcomes is attached.

What do you have to do?
We expect participants to attend **one online consensus meeting – via zoom (**please watch this video which explains what a consensus meeting is: https://www.youtube.com/watch?v=0R3SdX8nW-o).

During the meeting we would like participants to chat about the 23 outcomes and following discussion there will be **two polls** – we would like participants to vote on the outcomes for which there was no consensus in the survey – **the votes are anonymous**, so no one will be able to tell how you have voted. We will ask you to vote on each outcome on a scale from 1-9 (1–3, not important; 4–6, important; 7–9, critically important).

At the end of the meeting, there will be a **third and final poll** – we would like participants to choose one of 2 options for each outcome that reached consensus:

1. Mandatory to be included in the COS
2. Important but optional

We are doing a third poll because, although there are many outcomes which are very important, it is not easy to collect information on all of those in clinical trials. **We are aiming to have a group of 7-10 outcomes in the final Core Outcome Set for TN.**

Who will be at the meeting?
We will have a maximum of 15 participants (patients, doctors and researchers) and 4 members of the research team. We want to make sure we hear everyone's opinion.

Attached you can find the consent form, the meeting agenda, the list of 23 outcomes which will be up for discussion and voting, the list of outcomes which reached consensus and a glossary of terms. **Please complete the consent form and send it back to me before the 22nd April.**

Participants will receive a voucher for their time and invaluable input.

I will email you the Zoom link one or two days in advance. Please do not hesitate in contacting me should you have any questions about our study.

Best wishes. “

2. Consent form

TRINCOS: IRAS ID 240304 Sponsor Ref: B1262 F10153319 V 1.2 11 February 2022

Centre Number:

Study Number:

Participant Identification Number for this trial:

Title of Project: TRINCOS – DEFINING THE CORE OUTCOME SET FOR TRIGEMINAL NEURALGIA

Name of Researcher: Carolina Venda Nova

Please initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have these answered to my satisfaction. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. This will not affect my medical care or legal rights. ☐

3. I agree that relevant sections of my medical notes may be looked at by researchers, responsible individuals from regulatory authorities where it is relevant to my taking part in research, the sponsor University College London (UCL), and NHS Trust. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me might be used to support other research in the future and may be shared anonymously with other researchers. ☐

5. I agree to be contacted by letter/phone/email in case researchers need to clarify some information about my health. ☐

6. I agree that researchers use the data already collected for research even though I withdraw from the study. ☐

7. I agree to participate on an ONLINE consensus meeting, with other patients and with doctors. ☐

8. I agree to my General Medical Practitioner (GP) being informed of my participation in the study. ☐

9. I agree to being contacted about other trigeminal neuralgia studies. ☐

10. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

3. Glossary of terms

Consensus meeting	A meeting with a group of people who can contribute to a discussion that ultimately leads to a collective decision; in our research study this means, reaching a decision on the core outcome set for TN
Core outcome set	Group or list of outcomes that are used in all studies (clinical trials, for example) of a certain disease, usually decided when a group of people (patients, clinicians, and researchers) reach consensus
Delphi survey	A series of questionnaires completed by experts to reach consensus on a given subject. In our research study this means that a group of experts (patients, clinicians and researchers) voted on a list of 40 outcomes
Domain	Category to which an outcome belongs to, for example, pain intensity is included in the domain of PAIN and coping in the domain of COGNITIVE IMPACT
Facilitators	People who will lead the meeting, ensuring that it runs smoothly
Outcome measure	A tool used to assess the result of a treatment (treatment outcome), usually a paper questionnaire
Treatment Outcome	Result of a treatment (surgery or medication, for example)

4. Meeting agenda

AGENDA		
Time	**Topics**	**Lead by**
1pm	Welcome and introductions	Facilitators
1.15pm	Presentation: The TRINCOS project – past, present, and future	Carolina
1.30pm	Set up of group discussion 1	Carolina
1.35pm	Group discussion 1: group members will discuss outcomes for which no consensus was reached during the Delphi survey: Pain, Health Care Access, Physical and Emotional Impact	Facilitators
2.00pm	Poll 1 - voting on the first domains/outcomes	Participants
2.15pm	15-minute break	-
2.30pm	Results of first poll and discussion	Carolina
2.40pm	Set up of group discussion 2	Carolina
2.45pm	Group discussion 2 - group members will discuss outcomes for which no consensus was reached during the Delphi survey: Social and Cognitive Impact of pain	Facilitators
3.05pm	Poll 2 - voting on the last 5 domains/outcomes	Participants
3.20pm	10-minute break	-
3.30pm	Results of second poll and discussion	Carolina
3.40pm	Poll 3 - Finalizing the Core Outcome Set	All
4pm	End of the meeting	Carolina

5. List of outcomes – no consensus

List of outcomes that **DID NOT REACH CONSENSUS** in the online survey – these are the ones up for discussion and voting at the online meeting

We will ask you to vote on each outcome on a scale from 1-9 (1–3, not important; 4–6, important; 7–9, critically important)

Domain	Outcome	Text used on the online survey to clarify the meaning of each outcome
PAIN	**Pain free on medication**	How important is it that the treatment (medication or surgery) alleviates the pain completely, even if patients need to be on medication long-term
	Pain free off medication	How important is it that the treatment (medication or surgery) alleviates the pain completely, but patients can stop the medication after a while
	Quality of the pain	How important it is that the pain presents as a burning sensation
	Temporal aspects of pain	How important are the frequency and number of TN attacks over time
	Reduction in the need for rescue medication	How important is it that TN causes interference on one's daily life
	Trigger sensitivity	How important are the pain triggers (touching the face, a light breeze, or the wind)
EMOTIONAL IMPACT	**Depression**	How important it is to check whether TN can cause or have an impact on mood: depression refers to negative mood, loss of self-confidence, loss of motivation and enjoyment
	Anxiety	How important it is to check whether TN can cause or have an impact on mood: anxiety refers to worry, feeling fearful or restless
COGNITIVE IMPACT	**Catastrophising**	Checking whether TN can have an impact on one's thoughts - people are said to be catastrophising when they think that the worst will happen
	Illness Beliefs	Beliefs and feelings about TN (for example cause, consequences, symptoms)
	Self-efficacy	How important is one's trust on one's ability to deal with TN

Domain	Outcome	Text used on the online survey to clarify the meaning of each outcome
	Self-Efficacy to Manage Emotions	How important it is that patients have confidence to manage symptoms of anxiety, depression, disappointment, or anger
	Self-Efficacy for Managing Chronic Conditions	How important it is that patients have confidence in managing their tablets in challenging situations such as when travelling, when running low or when they have side effects
PHYSICAL IMPACT	**Self-care**	How important is it that TN pain impacts in the ability to look after oneself (washing, grooming, combing hair etc)
	Intimacy	How important is it that TN pain impacts on one's ability to be intimate with partners/spouses
SOCIAL IMPACT	**Work ability**	How important is it that TN has an impact on one's ability to perform normal work-related activities
	Effect of TN on family and friends	How important is it that TN has an impact on family, carers, and friends
	Avoidance behaviour	Patients might anticipate or avoid an unpleasant or painful situation (for example, avoidance of certain foods, activities, social interactions, etc).
	Social withdrawal and isolation	How important is it that patients withdraw from activities and isolate themselves due to TN
	Social validation	How important is it that family, friends, and colleagues understand TN
	Peer support	How important is it that TN patients speak to other patients and support each other
	Ability to Participate in Social Roles/Activities	How important is it that TN has an impact on one's ability to perform usual social roles and activities
	Time to return to work/family after surgery	How important it is to recover quickly from surgery
HEALTH CARE ACCESS	**Access to a specialist TN clinic*** **	How important it is to have access to a specialist TN clinic and ongoing health care support
	Patient's literacy about Trigeminal Neuralgia	How important is it that patients have a good understanding of trigeminal neuralgia: causes, prognosis, investigations, and treatment options

Domain	Outcome	Text used on the online survey to clarify the meaning of each outcome
	Literacy of GPs and dentists about TN* **	How important is it the level of doctors or dentist's knowledge about TN (symptoms, treatments, etc)
*** This outcome has reached consensus in all 3 groups, however, because it is not a clinical outcome (an outcome directly impacted by the treatment) it will be up for discussion during the meeting		

6. List of outcomes "in"

List of outcomes that were voted as **CRITICAL** by more than 70% of the participants in all groups (patients, clinicians, and researchers) in the online survey

Domain	Outcome	Text used on the online survey to clarify the meaning of each outcome
PAIN	**Pain relief**	How important it is that the pain reduces or alleviates
	Duration of pain relief	Length of time during which the pain is relieved by the treatment
	Pain intensity	How important is the intensity of the pain is or how much it hurts
	Quality of the pain	How important it is that the pain is electric shock like
	Pain interference	How important is it that TN causes interference on one's daily life
COGNITIVE IMPACT	**Fear of pain or fear of an attack**	How important it is to check whether fear of a TN attack is present even when the pain is controlled by treatment
	Coping	How important are coping mechanisms – ability to deal with stressful or difficult problems
PHYSICAL IMPACT	**Self-care**	How important is it that TN pain impacts in the ability to look after oneself (washing, grooming, combing hair etc)
	Eating	How important is it that TN pain impacts on the ability to eat comfortably
	Talking	How important is it that TN pain impacts on one's ability to talk
QUALITY OF LIFE	**Health related QOL**	How important is an individual's perceived well-being in physical, mental, and social aspects of health
GLOBAL IMPROVEMENT	**Overall response to treatment**	How important is it that patients feel better or worse on the whole following treatment, when compared to before treatment
SATISFACTION	**Satisfaction with treatment**	How important is it that a patient is satisfied with their treatment

SIDE EFFECTS OF TREATMENT	**Side effects of medication**	How important are the side effects of medication
	Side effects of surgery	How important are the side effects of surgery
HEALTH CARE ACCESS	**Literacy of GPs and dentists about TN**	How important is it the level of doctors or dentist's knowledge about TN (symptoms, treatments, etc)
	Access to a specialist TN clinic	How important it is to have access to a specialist TN clinic and ongoing health care support

Attrition rates between round 1 and round 2

	Round 1 only					Round 1 and 2					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Ability to participate in social roles and activities	6	7.3	1.0	83.3	0	75	7.5	1.1	88.0	0	0.668
Access to a specialist TN clinic	6	8.2	1.0	100.0	0	75	7.8	1.4	78.7	0	0.496
Anxiety	6	7.2	1.2	66.7	0	74	7.7	1.3	80.0	1	0.365
Avoidance behaviour	6	6.8	1.3	33.3	0	74	6.8	1.4	61.3	1	1.000
Catastrophising	6	6.8	1.9	66.7	0	73	6.5	1.8	57.3	2	0.697
Coping	6	7.2	1.5	66.7	0	75	7.4	1.1	85.3	0	0.678
Depression	6	7.2	1.2	66.7	0	74	7.7	1.3	80.0	1	0.290
Duration of pain relief	included only in R2 and R3										
Eating	6	7.7	1.0	100.0	0	75	8.2	1.0	94.7	0	0.242

	Round 1 only					Round 1 and 2					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Effect of TN on Family and friends	6	7.0	1.4	66.7	0	74	7.1	1.6	62.7	1	0.882
Fear of pain or fear of an attack	6	7.0	1.8	66.7	0	75	7.4	1.5	72.0	0	0.537
HRQOL	6	8.2	1.0	100.0	0	75	8.2	0.9	96.0	0	1.000
Illness beliefs	6	6.5	1.9	50.0	0	72	6.2	1.5	40.0	3	0.646
Intimacy	6	6.2	2.9	66.7	0	71	7.3	1.5	66.7	4	0.117
Literacy of GPs and dentists about TN	6	8.0	1.3	83.3	0	75	8.2	1.2	92.0	0	0.697
Overall response to treatment	6	7.8	0.8	100.0	0	75	8.0	1.1	92.0	0	0.665
Pain free off medication	5	6.8	1.6	33.3	1	73	7.4	1.8	65.3	2	0.471
Pain free on medication	5	6.6	1.5	33.3	1	73	7.4	1.4	69.3	2	0.222
Pain intensity	6	7.8	1.8	66.7	0	75	8.2	1.2	92.0	0	0.452

	Round 1 only					Round 1 and 2					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Pain interference	6	8.0	0.9	100.0	0	73	7.9	1.1	92.0	2	0.829
Pain relief	6	7.8	1.6	83.3	0	75	8.2	1.2	92.0	0	0.445
Patient's literacy about TN	6	7.3	2.0	66.7	0	75	7.8	1.2	86.7	0	0.355
Peer support	6	6.8	1.5	50.0	0	75	6.5	1.3	52.0	0	0.592
Quality of the pain - electric shock	5	7.0	1.6	50.0	1	73	7.9	1.4	84.0	2	0.172
Quality of the pain - constant burning	5	6.6	1.5	33.3	1	67	7.0	1.8	56.0	8	0.630
Reduction in the need for rescue medication	6	6.8	1.7	50.0	0	72	7.0	1.8	56.0	3	0.794
Satisfaction with treatment	6	7.8	1.3	83.3	0	74	7.7	1.3	84.0	1	0.857
Self-care	6	7.5	1.2	83.3	0	74	8.0	1.0	88.0	1	0.249
Self-efficacy	6	7.7	1.2	83.3	0	75	7.3	1.4	74.7	0	0.499

	Round 1 only					Round 1 and 2					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Self-efficacy on managing chronic conditions	6	6.7	1.8	50.0	0	74	7.5	1.4	76.0	1	0.191
Self-efficacy on managing emotions	6	6.5	2.1	50.0	0	75	7.2	1.4	70.7	0	0.260
Side effects of medication	6	7.3	1.0	83.3	0	75	7.7	1.2	86.7	0	0.430
Side effects of surgery	5	7.6	0.9	83.3	1	70	8.0	1.1	86.7	5	0.430
Social Validation	6	6.5	1.6	33.3	0	75	6.6	1.4	48.0	0	0.868
Social withdrawal and isolation	6	7.0	1.3	50.0	0	74	7.0	1.7	64.0	1	1.000
Talking	6	7.5	1.2	83.3	0	75	8.1	1.1	92.0	0	0.205
Temporal aspects of pain	6	7.5	1.5	83.3	0	74	7.4	1.4	77.3	1	0.867
Time to return to work/family responsibilities after surgery	included in R2 and R3 only										
Trigger sensitivity	6	6.7	1.6	50.0	0	72	7.5	1.5	73.3	3	0.215

	Round 1 only					Round 1 and 2					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Work ability	6	7.7	1.2	83.3	0	73	7.5	1.3	80.0	2	0.717
TN: trigeminal neuralgia; HRQOL: health related quality of life: n: number; SD: standard deviation; GP: General Practitioner											

Attrition rates between round 2 and round 3

	Round 1 and 2 only					Round 3					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Ability to participate in social roles and activities	5	7.8	0.4	100.0	0	70	7.5	1.0	88.6	0	0.509
Access to a specialist TN clinic	5	6.8	1.6	40.0	0	70	8.1	1.3	84.3	0	**0.037**
Anxiety	5	5.8	1.3	20.0	1	70	7.7	1.2	85.7	0	**0.001**
Avoidance behaviour	5	6.8	0.4	80.0	0	69	6.9	1.4	65.7	1	0.875
Catastrophising	5	5.0	2.6	20.0	0	70	6.8	1.6	65.7	0	**0.023**
Coping	5	6.8	0.8	60.0	0	70	7.5	1.2	85.7	0	0.205
Depression	5	6.0	1.4	40.0	1	70	7.9	1.1	87.1	0	**0.000**
Duration of pain relief	5	7.6	0.5	100.0	0	69	7.9	1.2	92.9	1	0.582
Eating	5	8.0	0.7	100.0	0	70	8.2	0.9	95.7	0	0.629

	Round 1 and 2 only					Round 3					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Effect of TN on Family and friends	5	7.2	1.1	80.0	0	69	7.0	1.6	60.0	1	0.785
Fear of pain or fear of an attack	5	6.6	0.9	40.0	0	70	7.5	1.5	77.1	0	0.191
HRQOL	5	8.0	0.7	100.0	0	70	8.3	0.9	97.1	0	0.469
Illness beliefs	5	5.2	1.6	20.0	0	69	6.4	1.4	51.4	1	0.071
Intimacy	5	7.0	1.8	40.0	0	68	7.4	1.4	71.4	2	0.547
Literacy of GPs and dentists about TN	5	8.4	0.5	100.0	0	70	8.3	1.2	92.9	0	0.854
Overall response to treatment	5	7.6	1.1	80.0	0	70	8.1	1.0	94.3	0	0.286
Pain free off medication	5	6.8	1.6	40.0	0	69	7.6	1.7	72.9	1	0.311
Pain free on medication	5	8.0	1.9	80.0	0	70	7.3	1.3	71.4	0	0.263
Pain intensity	5	8.4	0.5	100.0	0	70	8.3	1.2	94.3	0	0.854

	Round 1 and 2 only					Round 3					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Pain interference	5	8.0	1.0	100.0	0	69	8.1	0.9	94.3	1	0.812
Pain relief	5	7.8	1.1	80.0	0	70	8.4	1.1	95.7	0	0.242
Patient's literacy about TN	5	7.6	1.7	80.0	0	70	7.9	1.2	88.6	0	0.601
Peer support	5	6.2	1.9	40.0	0	70	6.8	1.2	65.7	0	0.303
Quality of the pain - electric shock	5	7.8	1.1	80.0	0	68	8.0	1.2	87.1	2	0.719
Quality of the pain - constant burning	5	6.8	1.9	60.0	0	64	7.2	1.6	58.6	6	0.597
Reduction in the need for rescue medication	5	6.2	1.8	40.0	0	68	7.0	1.7	58.6	2	0.315
Satisfaction with treatment	5	7.8	1.1	100.0	0	69	7.7	1.2	85.7	1	0.857
Self-care	5	8.0	1.2	80.0	0	69	8.0	1.0	90.0	1	1.000
Self-efficacy	5	7.0	2.0	60.0	0	70	7.3	1.3	78.6	0	0.632

	Round 1 and 2 only					Round 3					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Self-efficacy on managing chronic conditions	5	7.0	2.0	60.0	0	69	7.6	1.4	78.6	1	0.371
Self-efficacy on managing emotions	5	6.8	1.9	60.0	0	70	7.1	1.3	74.3	0	0.630
Side effects of medication	5	6.8	1.6	40.0	0	70	7.8	1.2	88.6	0	0.082
Side effects of surgery	4	7.5	1.9	60.0	1	65	8.0	1.1	88.6	5	0.401
Social Validation	5	6.0	1.0	40.0	0	70	6.7	1.3	54.3	0	0.243
Social withdrawal and isolation	5	6.8	0.4	80.0	0	69	7.1	1.7	68.6	1	0.697
Talking	5	8.2	0.8	100.0	0	69	8.1	1.0	91.4	1	0.828
Temporal aspects of pain	5	7.2	1.5	80.0	0	69	7.5	1.4	78.6	1	0.646
Time to return to work/family responsibilities after surgery	3	6.7	2.1	20.0	2	64	6.7	1.5	51.4	6	1.000
Trigger sensitivity	5	7.2	1.3	60.0	0	68	7.6	1.5	80.0	2	0.564

	Round 1 and 2 only					Round 3					
Outcome	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	n	mean	SD	%Classifying outcome as critical (7-9)	n scored as 10	*p*-value
Work ability	5	8.6	0.5	100.0	0	69	7.4	1.1	78.6	1	**0.019**
TN: trigeminal neuralgia; HRQOL: health related quality of life: n: number; SD: standard deviation; GP: General Practitioner											

APPENDIX 5 - Published articles arising from the present thesis

- Venda Nova C, Zakrzewska JM, Riordain RN, Baker SR. “They could have cut my head off and I wouldn’t have cared” - A qualitative study of patients’ experiences and the impact of trigeminal neuralgia. J Oral Facial Pain Headache 2022 Nov 28.
- Venda Nova C, Riordain RN, Baker SR, Zakrzewska JM. An international Delphi survey and consensus meeting to define the core outcome set for trigeminal neuralgia clinical trials. Eur J Pain. 2022 Sep 21
- Venda Nova C, Riordain RN, Baker SR, Zakrzewska JM. Looking beyond the obvious: the importance of outcomes and outcome measures in trigeminal neuralgia PAIN 2021; 162:2456 (Letter to the Editor)
- Venda Nova C, Zakrzewska JM, Baker SR, Ni Riordain R. Patient reported outcome measures in trigeminal neuralgia - A systematic review of psychometric performance. Eur J Pain. 2021;25
- Venda Nova C, Zakrzewska JM, Baker SR, Ni Riordain R. Treatment Outcomes in Trigeminal Neuralgia - A Systematic Review of Domains, Dimensions and Measures. World Neurosurg X. 2020;6

APPENDIX 6 - Poster presentations arising from the present thesis

- Venda Nova C, Ni Riordain R, Baker SR, Zakrzewska JM “What are the outcomes that matter to Trigeminal Neuralgia stakeholders? Results of an international Delphi survey.” International Association for the Study of Pain, Toronto, September 2022
- Venda Nova C, Zakrzewska JM, Ni Riordain R, Baker, SR. “A qualitative study of trigeminal neuralgia patients' lived experiences and desired outcomes of treatment” European Pain Federation, Dublin, April 2022
- Venda Nova C, Ni Riordain R, Baker SR, Zakrzewska JM “Outcomes of treatment and psychometric performance of patient reported outcomes in Trigeminal Neuralgia - Two Systematic Reviews”. International Headache Congress, September 2021