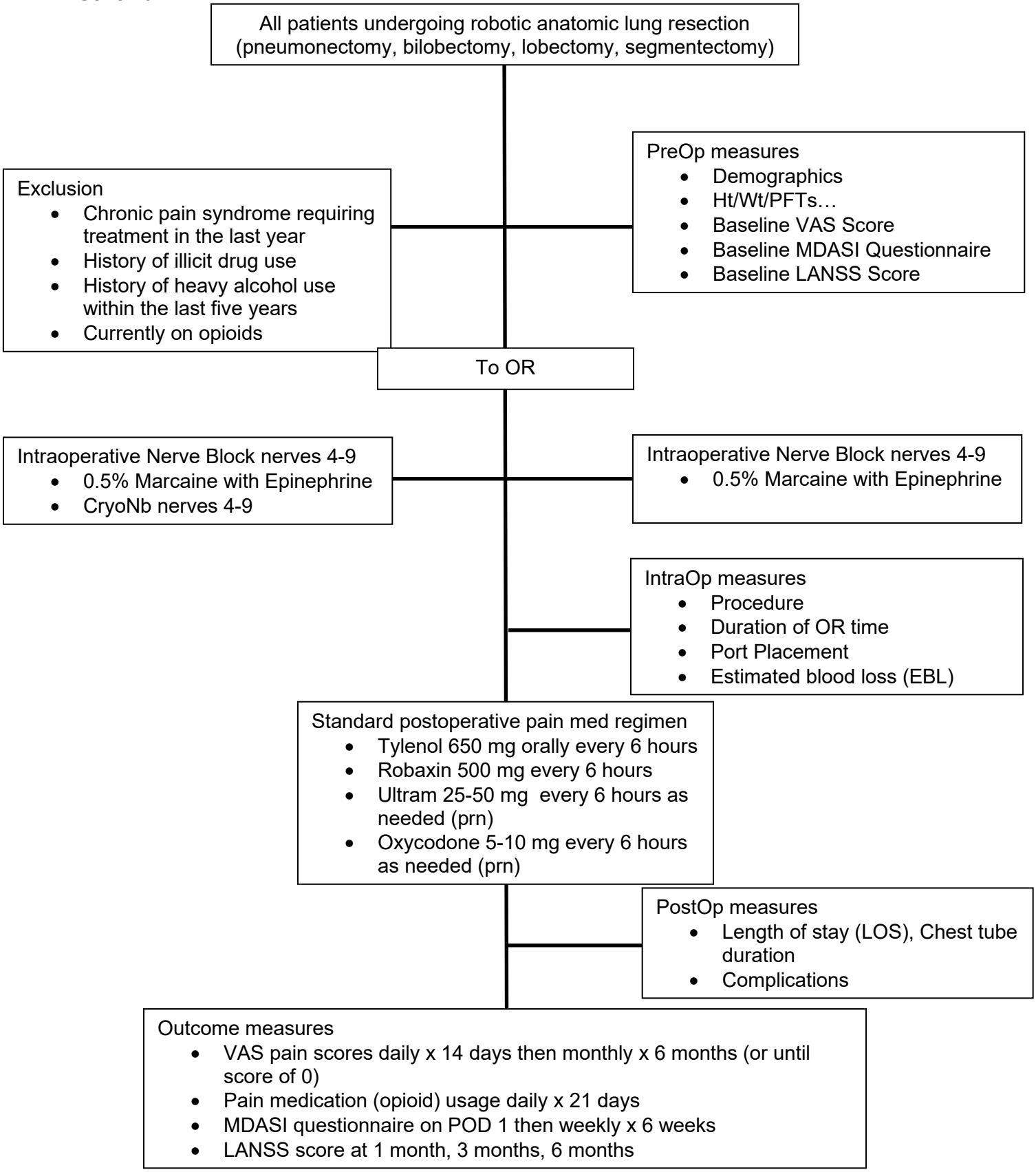
Efficacy of Intercostal CryoAnalgesia in Patients Undergoing Robot Assisted Anatomic Lung Resection

PROTOCOL SUMMARY

Synopsis

Title:	Efficacy of Intercostal CryoAnalgesia in Patients Undergoing Robot Assisted Anatomic Lung Resection
Short Title:	CryoNB in Robotic Lung Resection
Study Design:	Prospective randomized study
Study Objectives:	The objectives are to determine if the addition of Cryo Nerve Block at the time of robot assisted thoracoscopic lung resection surgery will: • Allow for improved postoperative analgesia as measured using Visual Analogue Scale (VAS) pain scores • Allow for decreased post-operative pain medication (opioid) use • Allow for accelerated recovery as measured by patient reported M.D. Anderson Symptom Inventory (MDASI) Questionnaire • Increases the risk for development of neurogenic pain as measured by the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale
Number of Subjects:	40 (20 in each group)
Sites:	Single site – Froedtert Hospital/Medical College of Wisconsin Single surgeon – Mario Gasparri, MD
Study Population:	Patients undergoing robot assisted thoracoscopic anatomic lung resection (pneumonectomy, bilobectomy, lobectomy or segmentectomy)
Inclusion Criteria:	• Age 18 - 85 years male or female • Acceptable surgical candidate • Willing and able to return for scheduled follow-up visits
Exclusion Criteria:	• Patients undergoing or requiring conversion to thoracotomy • Patients with chronic pain syndromes requiring treatment within the last year • Patients with a history of illicit drug use • Patients with a history of heavy alcohol use in the last five years as determined by the principal investigator • Patients currently using opioids
Participant Duration:	Six months
Study Endpoints:	Primary endpoints • Visual Analogue Scale (VAS) Pain score on post-operative days 1-14, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180 (or until a score of 0). • Pain medication use daily for 21 days post-operatively Secondary endpoints • M.D. Anderson Symptom Inventory Questionnaire on post-operative Day 1, Day 7, Day 14, Day 21, Day 30, Day 35, and Day 42 • Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score at Post-Operative Day 30, Day 90, and Day 180

Schema


All patients undergoing robotic anatomic lung resection (pneumonectomy, bilobectomy, lobectomy, segmentectomy)
Exclusion
Chronic pain syndrome requiring treatment in the last year
History of illicit drug use
History of heavy alcohol use within the last five years
Currently on opioids
PreOp measures
Demographics
Ht/Wt/PFTs…
Baseline VAS Score
Baseline MDASI Questionnaire
Baseline LANSS Score
To OR
Intraoperative Nerve Block nerves 4-9
0.5% Marcaine with Epinephrine
CryoNb nerves 4-9
Intraoperative Nerve Block nerves 4-9
0.5% Marcaine with Epinephrine
IntraOp measures
Procedure
Duration of OR time
Port Placement
Estimated blood loss (EBL)
Standard postoperative pain med regimen
Tylenol 650 mg orally every 6 hours
Robaxin 500 mg every 6 hours
Ultram 25-50 mg every 6 hours as needed (prn)
Oxycodone 5-10 mg every 6 hours as needed (prn)
PostOp measures
Length of stay (LOS), Chest tube duration
Complications
Outcome measures
VAS pain scores daily x 14 days then monthly x 6 months (or until score of 0)
Pain medication (opioid) usage daily x 21 days
MDASI questionnaire on POD 1 then weekly x 6 weeks
LANSS score at 1 month, 3 months, 6 months

HYPOTHESIS
The addition of Cryo Nerve Block to a standard postoperative pain regimen will improve analgesia and facilitate recovery following robot assisted thoracoscopic anatomic lung resection

SPECIFIC AIMS
This study will determine if the addition of Cryo Nerve Block during robot assisted thoracoscopic anatomic lung resection surgery will:

PRIMARY ENDPOINTS:
- Allow for improved postoperative analgesia as measured using Visual Analogue Scale (VAS) pain scores
- Allow for decreased post-operative pain medication (opioid) usage

SECONDARY ENDPOINTS:
- Allow for accelerated recovery as measured by patient reported M.D. Anderson Symptom Inventory (MDASI) Questionnaire
- Increases the risk for development of neurogenic pain as measured by the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale

RATIONALE FOR THE PROJECT
Thoracic surgical procedures are consistently reported to be among the most painful surgical incisions currently used.[1] Trauma to the skin, muscle, intercostal nerves, bones and pleura all contribute and lead to activation of various pain pathways including somatic, visceral, neurogenic and phrenic.[1] In the short term, this pain leads to ineffective cough and pulmonary hygiene resulting in respiratory complications and prolonged hospital stays while in the longer term it leads to prolonged recovery, delayed return to work and in some instances, chronic post thoracotomy pain syndromes.[2] Minimally invasive approaches such as standard thoracoscopy or robotic assisted thoracoscopy have certainly decreased some of this trauma as evidenced by decreased length of stays and decreased complication rates however even with these minimally invasive techniques, recovery to 80% of baseline is 25 days[3] and 9.4% of patients are still using narcotics after 90-180 days.[4]

Several options are available in the management of pain following thoracic surgery with a multimodal pain medicine approach being most common. Opioids, unfortunately, are a relatively large part of this approach and are often relied upon despite their relatively unfavorable adverse event profile and risk for addiction. Many of the other pain adjuncts often used with thoracotomies such as epidural catheters or intraoperatively placed pain catheters are not really reasonable when using minimally invasive approaches as the hospital length of stay is 1-2 days. Intercostal cryoanalgesia has been shown to be a safe and effective strategy for post-operative pain management in patients undergoing thoracotomy.[5,6] Recent studies have demonstrated the beneficial effect of cryoanalgesia for post-thoracotomy pain in reduction of opioid requirement, reduction in post-operative pain scores, and superior pulmonary function (higher FEV1 and FVC values)[5] and that it can produce temporary neurolysis for up to two months without long-term histological nerve damage.[6] To date it has not been studied when using minimally invasive techniques whether it be standard thoracoscopy or robotic assisted thoracoscopy but it would stand to reason that it would be equally or maybe more effective in this patient population and truly maximize the benefits of a minimally invasive approach .

We therefore propose to assess whether intra-operative intercostal cryoanalgesia using the cryoICE® probe provides superior post-operative analgesia as compared to our current standard pain management strategy in patients undergoing robotic assisted thoracoscopic anatomic lung resection and allows for decreased opioid use and more rapid recovery.

PROJECT DESIGN AND PROTOCOL

DESIGN

This is a single center, single surgeon, prospective, randomized trial examining the addition of Cryo Nerve Block during robot assisted thoracoscopic anatomic lung resection surgery

SUBJECTS IN THE STUDY

40 total subjects will be enrolled in the study – 20 in each group

Inclusion Criteria

- Patients undergoing robot assisted thoracoscopic anatomic lung resection surgery
- Male or female age 18 or older
- Acceptable surgical candidate
- Willing and able to return for scheduled follow-up visits

Exclusion Criteria

- Patients undergoing or requiring conversion to thoracotomy
- Patients with chronic pain syndromes requiring treatment in the last year
- Patients with a history of illicit drug use
- Patients with a history of heavy alcohol use in the last five years as determined by the principal investigator
- Patients currently using opioids

CONSENT

All patients eligible for this study will be approached for consent to enter the study in compliance with Human Research Review Committee (HRRC) standards. Consent will be obtained by the principal investigator or authorized delegate.

RANDOMIZATION PROCESS

Following the attainment of consent to enter the study, patients will be randomized to either the standard postoperative pain regimen or the standard postoperative pain regimen plus cryo nerve block by a blinded procedure where a card indicating either group will be drawn in a witnessed setting by a noninvestigator.

PROCEDURE

All patients will be assessed at baseline and then taken to the operating room for robot assisted thoracoscopic anatomic lung resection surgery. Each operation will be performed by the same surgeon and port placement will be identical (aside from laterality) in each patient. All patients will have the first two ports placed at which time an intercostal nerve block of nerves 4-9 will be performed using 0.5% Marcaine with Epinephrine. Additionally, in the study group, Cryo Nerve Block of nerves 4-9 will also be performed. To perform the cryo nerve block the 18 inch Atricure® cryoSPHERE Probe will be used in each case. The remaining ports will then be placed, the robot docked, and the procedure performed. Following the procedure, a chest tube will be placed through the camera port. Postoperatively, all patients will receive the standard post-operative pain regimen currently used by the Thoracic Surgery Service at Froedtert Hospital/Medical College of Wisconsin which consists of Tylenol and Robaxin around the clock and Ultram as first line analgesia for breakthrough pain and Oxycodone as the second line agent if necessary.

RISKS AND PRECAUTIONS

The pain management strategy outlined above, whether with or without cryo nerve block, is the current standard pain management strategy following robot assisted thoracoscopic lung

resection surgery at Froedtert Hospital/Medical College of Wisconsin. Both are routinely employed and it must be stressed that neither arm is experimental in any way with both modalities currently in use and being used successfully. What is unclear at present is which approach offers greater advantage to the patient in terms of improved analgesia and facilitation of recovery.

Risks inherent to this study are those associated with the operative procedure of robot assisted thoracoscopic lung resection surgery. To date there have been no reports of acute adverse events with cryo nerve block.

DATA COLLECTED
As shown in the schema, the following data will be collected

Preoperatively – within 30 days of surgery
- Characteristics (Age, gender, race, marital status, ECOG function, height, weight, BMI, tobacco use, major comorbidities)
- Baseline VAS Score
- Baseline MDASI
- Baseline LANSS

Intraoperatively – at time of surgery
- Procedure
- Procedure duration
- Port placement
- Intraoperative complications
- Estimated blood loss (EBL)

Postoperatively – at designated time points
- Length of stay
- Chest tube duration
- Complications
- VAS pain scores daily on post-operative Days 1-14, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180 (or until score of 0).
- Pain med usage daily for post-operative Days 1-21
- MDASI questionnaire on post-operative Day 1, Day 7, Day 14, Day 21, Day 30, Day 35, and Day 42
- LANSS score at at Day 30, Day 90 and Day 180

A time frame of data collection points is shown below and the VAS scale, MDASI Questionnaire, and LANSS pain scale are included in the appendix.

Day	Characteristics	VAS	MDASI	LANSS	Pain meds
Baseline	X	X	X	X	X
0					
1		X	X		X
2		X			X
3		X			X
4		X			X

5		X			X
6		X			X
7		X	X		X
8		X			X
9		X			X
10		X			X
11		X			X
12		X			X
13		X			X
14		X	X		X
15					X
16					X
17					X
18					X
19					X
20					X
21			X		X
22					X
30 (+/- 2 days)		X	X	X	
35 (+/- 2 days)			X		
42 (+/- 2 days)			X		
60 (+/- 5 days)		X			
90 (+/- 5 days)		X		X	
120 (+/- 5 days)		X			
150 (+/- 5 days)		X			
180 (+/- 5 days)		X		X	

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1. Marshall K, McLaughlin K. Pain Management in Thoracic Surgery. Thorac Surg Clin 2020;30(3):339-346

2. Niraj G, Kelkar A, Kaushik V, et al. Audit of postoperative pain management after open thoracotomy and the incidence of chronic postthoracotomy pain in more than 500 patients at a tertiary center. J Clin Anes 2017;36:174-177

3. Fagundes CP, Shi Q, Vaporciyan AA, et al. Symptom recovery after thoracic surgery: Measuring patient-reported outcomes with the MD Anderson Symptom Inventory. J Thorac Cardiovasc Surg 2015;150:613-9

4. Brescia AA, Harrington CA, Mazurek AA, et al. Factors associated with new persistent opioid usage after lung resection. Ann Thorac Surg 2019;107(2):363–868

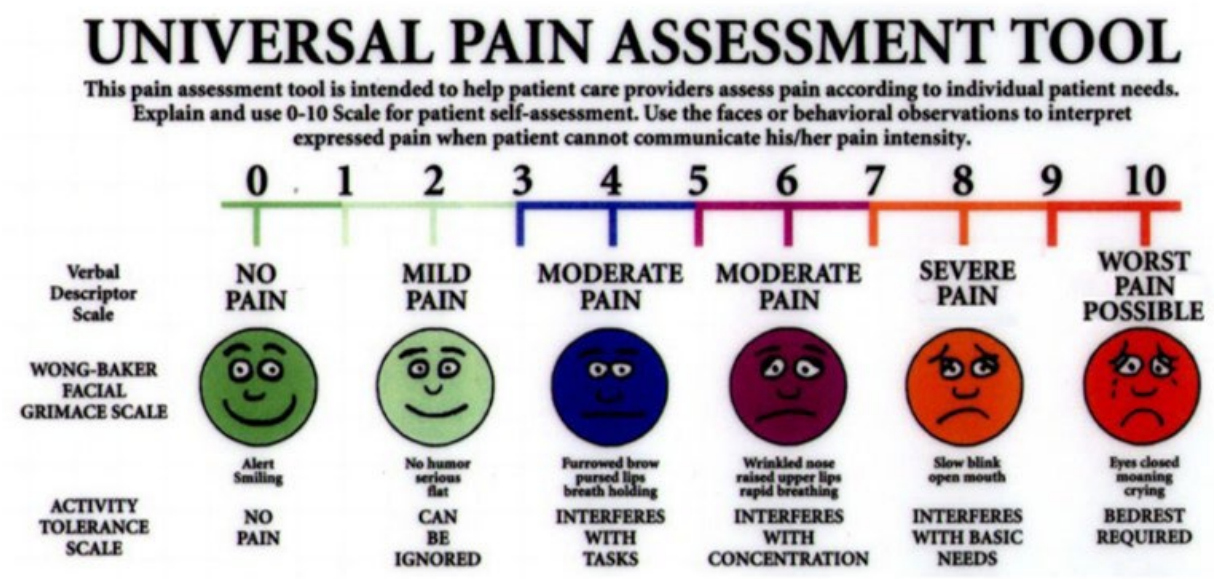
5. Sepsas E, Misthos P, Anagnostopulu M, et al. The role of intercostal cryoanalgesia in post-thoracotomy analgesia. Interact Cardiovasc Thorac Surg 2013;16:814-818

6. Moorjani N, Zhao F, Tian Y, et al. Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostal nerves: a human prospective randomized trial and a histological study. Eur J Cardiothorac Surg 2001;20:502-507.

APPENDIX I - Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

APPENDIX II – Visual Analogue Scale Pain Score



Appendix III – MD Anderson Symptom Inventory (MDASI) Questionnaire

M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Appendix IV – Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale

The S-LANSS Pain Score

1.	**In the area where you have pain, do you also have "pins and needles", tingling or prickling sensations?**	
	☐ NO – I don't get these sensations	0
	☐ YES – I get these sensations	5
2.	**Does the painful area change colour (perhaps look mottled or more red) when the pain is particularly bad?**	
	☐ NO – The pain does not affect the colour of my skin	0
	☐ YES – I have noticed that the pain does make my skin look different from normal.	5
3.	**Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.**	
	☐ NO – The pain does not make my skin abnormally sensitive to touch.	0
	☐ YES – My skin in that area is particularly sensitive to touch.	3
4.	**Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like "electric shocks", jumping and bursting might describe this.**	
	☐ NO – My pain doesn't really feel like this.	0
	☐ YES – I get these sensations often.	2
5.	**In the area where you have pain, does your skin feel unusually hot like a burning pain?**	
	☐ NO – I don't have burning pain	0
	☐ YES – I get burning pain often	1
6.	**Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?**	
	☐ The painful area feels no different from the non-painful area	0
	☐ I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area.	5
7.	**Gently press on the painful area with your finger tip and then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?**	
	☐ The painful area does not feel different from the non-painful area.	0
	☐ I feel numbness or tenderness in the painful area that is different from the non-painful area.	3
	Total score:	

Scoring a score of 12 or more suggests pain of predominantly neuropathic origin

Source: Bennett, M *et al* J Pain, Vol 6, No 3 March, 2005 pp 149–158 The S-LANSS Score for Identifying Pain of Predominantly Neuropathic Origin: Validation for Use in Clinical and Postal Research.