

**Cost-effectiveness and Quality of Life after Treatment of
Lumbar Spinal Stenosis with the Interspinous Distractor
Device (X-Stop) or Laminectomy:**

A Randomised Control Trial

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2017

Submission for MD Res

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

Abbreviations

CELAX	Cost effectiveness and Quality of Life after treatment of Lumbar Spinal Stenosis with the Interspinous Distractor Device (X Stop) or Laminectomy
DALY	Disability adjusted life year
FBSS	Failed Back Surgery Syndrome
HRG	Healthcare Resource Group
ICER	Incremental cost-effectiveness ratio
ICD10	10th revision of the International Statistical Classification of Diseases
IDD	Interspinous distractor device
LSS	Lumbar spinal stenosis
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OPCS4	Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4
PbR	Payment by Results
PLICS	Patient Level Information and Costing System
QALY	Quality adjusted life year
RCT	Randomised Control Trial
SPORT	Spine Patient Outcomes Research Trial
TGF β 1	Transforming Growth Factor Beta 1

Abstract

Lumbar Spinal Stenosis (LSS) is becoming increasingly prevalent in the ageing population and surgery is regarded as the gold standard treatment after conservative measures have failed. Many patients do not improve however, and the complication rates are high. Interspinous distraction devices (IDDs) have been proposed as a safe alternative however their cost and their failure rate has made their use controversial. No UK data exists to date with regards to the cost-effectiveness of the surgical management of IDD in LSS and there is a lack of long term follow up.

Objective – To determine the cost-effectiveness and quality of life after the treatment of LSS with the X-Stop device and laminectomy.

Method – A randomised control trial of 47 patients with LSS (26 laminectomy and 21 X-Stop). The primary outcome was cost and quality of life measured using EQ5D. Other clinical outcomes were measured using SF36, ZCQ, ODI and QBPDS. Secondary measures included, operating time, length of stay and complication rates. Patients were followed up at 6 months, 12 months and 24 months.

Results – The mean cost of the Laminectomy group was £2,711.8 and the mean cost of the X-Stop group was £5,148 (£1,799 plus the cost of the device £2,605 per device). Using intention to treat analysis, the mean QALY gain for the laminectomy group was 0.92 and for the X-Stop group was 0.81. The incremental cost effectiveness ratio was £-22,247.27. The complication rate for the laminectomy group was 19.2% vs 9.5% for the X-Stop group.

Conclusion – Laminectomy is more cost-effective than X-Stop insertion for the treatment of LSS, mainly due to the cost of the device. The X-Stop device does not replace a laminectomy as gold standard treatment however it should be considered when a less invasive procedure is required.

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Introduction

Background

This dissertation presents the results of the CELAX trial. This is a randomised control trial comparing the cost effectiveness of laminectomy and the interspinous distractor device X-stop as treatment of Lumbar spinal stenosis(LSS). The study also addresses the quality of life of patients suffering with this condition and how it is affected by the two different types of treatment.

The use of interspinous distractor devices (IDDs) in the management of lumbar spinal stenosis (LSS) is controversial. Decompressive lumbar laminectomy is accepted as the gold standard for surgery; however, due to the morbidity associated with this invasive surgical treatment and the higher complication rate in the elderly population, laminectomy may not always be the best option.

In 2005, the X-Stop^(R) Interspinous Process Decompression System^(R) (Medtronic Spine LLC) was the first IDD to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of LSS. This device was designed to provide relief of the symptoms of neurogenic claudication from LSS via a minimally invasive approach. The procedure time is much shorter, carries fewer risks of complications and is also reversible, i.e. the device can be removed. X-stop became popular in the management of LSS however it is more expensive than a lumbar laminectomy. The objective of this study was to elucidate whether the device is cost-effective when compared to the standard treatment, laminectomy, and to find out if and how it influences quality of life.

Lumbar Spinal Stenosis (LSS)

Introduction

Lumbar spinal stenosis (LSS) is the commonest degenerative condition of the lumbar spine. It causes the symptoms of neurogenic claudication and is the commonest cause of back and leg pain in the over fifties. It affects mainly the elderly population and is a detriment to the quality of life of the sufferers. It consumes large amounts of healthcare resources and is a common reason for GP consultations and referrals thereby being a costly burden to the national health service.

Definition

LSS can be defined as narrowing of the spinal canal which causes compromise of the neural and vascular structures. The definition of this common condition can be broad, including any cause of narrowing of the spinal canal, nerve root canal or intervertebral foramina. This can be classified as local, segmental or generalized, or caused by bone or soft tissue. Although the spinal canal could be congenitally narrow, the term LSS is generally accepted to refer to the acquired type with the leading cause being age-related change where acquired changes including degenerative disc disease, ligamentum flavum thickening and facet joint hypertrophy compete for space with the neural structures thereby resulting in symptoms of neurogenic claudication. Classically, the patient presents with a history of leg pain, which improves or resolves with flexion such as sitting or bending forward.

LSS is confirmed radiologically. A diameter of 11.5mm or a canal area less than 1.5cm² has been used by some authors to define LSS,ⁱ however there is no universally agreed cut-off canal diameter or other anatomical measurements that define stenosis. The appearance of a narrow canal with reduced CSF space around the thecal sac in a symptomatic patient confirms the diagnosis more reliably. MRI is the best modality to diagnose LSS as it not only demonstrates the size of the spinal canal but can also confirm the main culprit of the stenosis such as infolding of the ligaments, facet joint hypertrophy and whether there is concurrent neuroforaminal narrowing.ⁱⁱ

In addition to the above LSS can be further subdivided into central canal stenosis and lateral recess stenosis. The lateral recess is defined as the area of the spinal canal between the medial point of the facet up to the neuroforamen where the exiting nerve root is normally located. The severity of LSS has also been described to be mild if less than a third of the calibre of the spinal canal is reduced, moderate if less than two thirds but more than one third of the area is affected and severe if more than two-thirds of the spinal canal area is reduced.

Lumbar Spine Anatomy

In the lumbar spinal canal, the spinal cord terminates at the upper border of the L2 vertebra as the conus medullaris continuing down as the cauda equina. The nerve roots of the cauda equina are enclosed in the thecal sac and at each level the corresponding nerve roots branch out and traverse the intervertebral neuroforamen. The average anterior posterior diameter of the normal lumbar canal ranges from 15mm to 27mm.ⁱⁱⁱ This varies with

posture. The diameter is wider in the flexed position and narrower in the extended position. This is an important physiological feature as patients tend to get a relief of their symptoms when they bend forward.

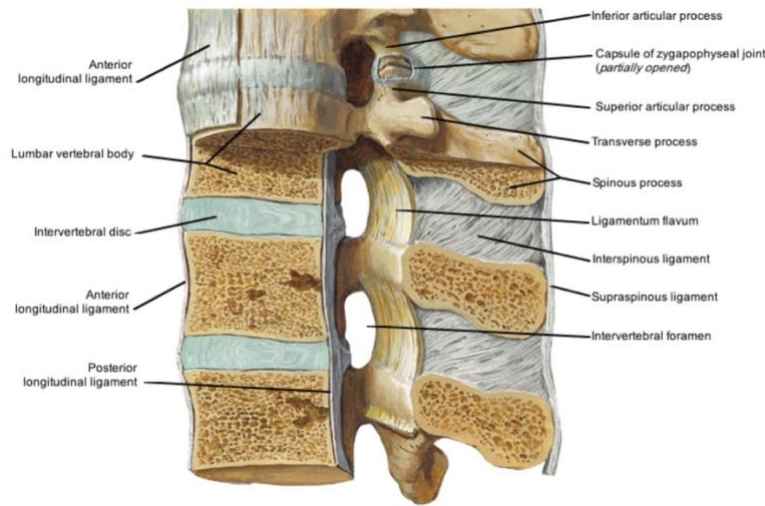


Figure 1 - Anatomy of the lumbar spine and spinal ligaments. Netter 2006, Plate 158

The vertebral bodies of the spine articulate with each other through the facet joints. (Fig. 1) The facet joints (zygapophyseal) are synovial joints in between the vertebral bodies that allow the articulating spine to move whilst maintaining stability. The articulating surfaces involved are the inferior facet of the vertebra above and the superior facet of the lower vertebra. There are two facet joints, right and left, at each spinal level. Like any other synovial-lined joint there is a fibrous capsule enclosing synovial fluid and the articulating surfaces are lined by cartilage. In the lumbar spine these joints carry a greater axial load than in the rest of the spine making these motion segments more at risk of degeneration. The orientation of the facet joints in the lumbar spine is oblique. In the sagittal plane the joint line produces an average angle of 170 degrees and in the horizontal plane it ranges from 25 degrees at L2 to 50 degrees at L5. This contributes to the curvature in the lumbar spine known as lordosis. (Fig. 2) ^{iv}

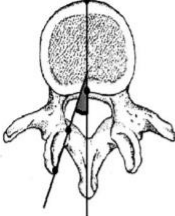
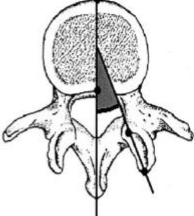
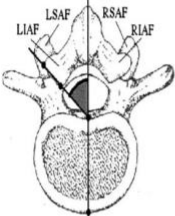
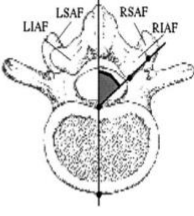
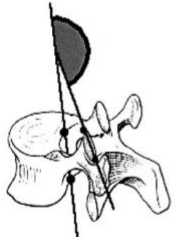
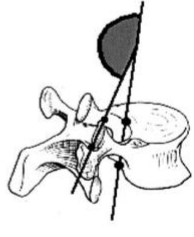
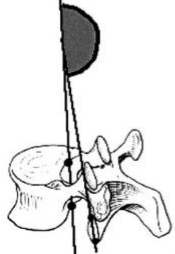
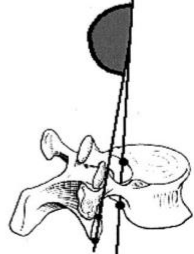
Measurements Left	Illustrations Right	Measurement definitions
M21: LSTFA 	M22: RSTFA 	Superior transverse facet angles: The angles, in the transverse plane, between the lines of the superior facets widths and superior vertebral body length
M23: LITFA 	M24: RITFA 	Inferior transverse facet angles: The angles, in the transverse plane, between the lines of the inferior articular facets widths and inferior vertebral body length
M25: LSLFA 	M26: RSLFA 	Superior longitudinal facets angles: The superior angles, in the sagittal plane, between the lines of the superior facets lengths and posterior vertebral body height
M27: LILFA 	M28: RILFA 	Inferior longitudinal facets angles: The superior angles, in the sagittal plane, between the lines of the inferior facets lengths and posterior vertebral body height

Figure 2 - Illustration of superior and inferior facet angles in the transverse and sagittal planes. From Masharawi et al.^v

The intervertebral fibrocartilaginous discs are located between each vertebral body. The intervertebral discs are very important in spine mobility and flexibility. They act as shock absorbers during load transmission and facilitate flexion, extension and rotation of the human spine. They are cartilaginous structures composed of a tough outer annulus fibrosus and soft inner nucleus pulposus. The latter is composed of type II collagen and elastic fibres embedded in a soft hydrated matrix of proteoglycans (a type of glycosaminoglycan) whereas the annulus is composed of mainly collagen type II fibres organised in concentric circles forming 15-20 lamellae. The disc lies in between the cartilaginous end-plates of the vertebral bodies above and below. The young healthy disc receives

very little blood supply and only receives some innervation to the outer annulus. Both within the nucleus and the annulus there are interspersed cells which are chondrocyte-like in the nucleus and more fibroblast-like in the annulus. These cells are responsible for secreting collagen type II fibres and the proteoglycans that make up the extracellular matrix. The main glycosaminoglycan in the nucleus pulposus is Aggrecan which is very hydrophilic and acts as an osmotic agent by drawing water in and is what maintains the healthy disc hydrated. There is a constant breakdown and synthesis of these proteoglycans, forming a dynamic extracellular matrix. Metalloproteinase enzymes synthesised by the cells in the nucleus pulposus is what breaks down these matrix macromolecules. The balance of breakdown and synthesis is what maintains the disc's integrity. (Fig. 3)

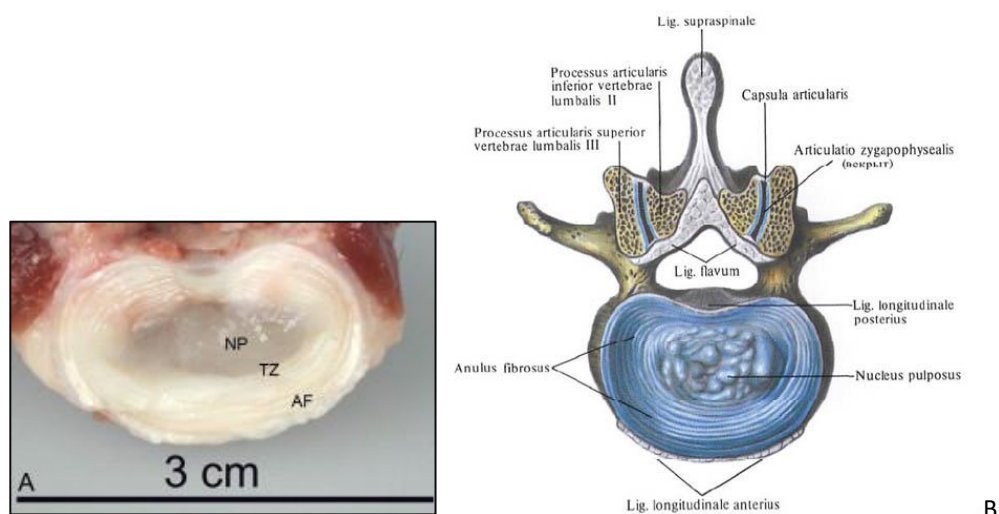


Figure 3 – Cross section through a lumbar intervertebral disc. A histological section – NP- nucleus pulposus, TZ – transitional zone, AF – annulus fibrosus. B – schematic diagram.

The vertebral column is reinforced with ligaments that help support the spine and which act like a natural brace. These include the anterior and posterior longitudinal ligaments, ligamentum flavum, the interspinous ligaments and the supraspinous ligament.

The anterior and posterior longitudinal ligaments, respectively, run anterior and posterior to the vertebral bodies throughout the entire length of the spine. These ligaments appear to be long continuous bands but in effect they have an attachment to each vertebral body. Their role is to prevent forward or backward movement of one vertebral body on top of another. They also restrict excessive movement such as hyper-extension or hyper-flexion.

Ligamentum flavum is another reinforcing structure which runs inside the spinal canal posterior to the spinal cord and thecal sac and anterior to the spinous process. It is composed of yellow elastic tissue and extends out laterally to the root of the articular processes and the ligaments on both sides which also meet at the midline. This ligament is broadest in the lumbar spine and plays an important role in the pathophysiology of LSS (see below).

The interspinous ligaments run from one spinous process to another. They extend from the root to the apex of each process and are well developed in the lumbar spine but only slightly developed in the cervical spine.

The supraspinous ligament connects the apices of adjacent spinous processes. It runs from the seventh cervical vertebra down to the sacrum and is continuous with the interspinous ligament in between the spinous processes. It is a strong fibrous cord that acts as a tension band and is very important in spinal stability. (Fig. 1)

Biomechanics of the Lumbar spine

The effects of the forces imparted on the lumbar spine depend significantly on the individual geometry such as height and stature and lordotic curvature. There is also variability between different spine levels depending on the alignment of the facets, discal height and vertebral body dimensions. L4/5 and L5/S1 are the spinal levels most commonly affected by degenerative disease commonly referred to as 'wear and tear' and they are also the levels experiencing higher compressive forces as found by various cadaver and spine models.^{vi} In addition to this, posture has been shown to influence the biomechanics of the lumbar spine. Forward flexion is related to an increase in the diameter of the spinal canal, it also caused increased strain on the spinal ligaments. Extension on the other hand reduces the calibre of the spinal canal and causes increased pressure on the facet joints which resist horizontal movement of the vertebral bodies.^{vii}

Pathophysiology of Degenerative Lumbar Spinal Stenosis

As part of the normal ageing process the spine is affected by degenerative changes. These acquired changes can become pathological and alter the structure of the spine. Common changes seen in the elderly spine include ligament hypertrophy, disc degeneration and herniation and facet joint arthritis. With wear and tear the supporting spinal ligaments become hypertrophied. As tissues become less elastic with ageing, ligamentum flavum especially, starts to buckle and becomes thicker. The intervertebral discs become dehydrated and lose height. Annular tears acquired over time cause bulging of the nucleus pulposus and protrusion into the spinal canal. This resultant loss of intervertebral height, causes infolding of the ligaments further exacerbating the crowding in the canal. The synovial facet joints commonly form osteophytes as part of a reactive osteoarthritic process and the articular facets enlarge and hypertrophy. All the above changes cause the spinal canal in the lumbar spine to lose calibre and as a result compete for space with the traversing neural structures. As the thecal sac containing the spinal nerve roots becomes enclosed in an increasingly narrow canal there is resultant compression of these nerve roots. This neural compression results in the symptoms of neurogenic claudication. Often nerve compression causes swelling and inflammation of the affected nerve further exacerbating the problem.

Another contributing factor to canal narrowing is spondylolisthesis. This is acquired slippage of one vertebral body on top of another. It can occur with various degrees of severity and is also caused by degenerative changes in the spine.

As mentioned above, the diameter of the lumbar spinal canal changes with posture. During extension of the lumbar spine the spinal canal has a smaller calibre than when the lumbar spine is in the flexed position. Due to this fact, the symptoms of neurogenic claudication classically vary with posture and activity. Often the symptoms improve when the spine is in a flexed position such as when the patient bends forward or when sitting.

The Ageing Process in the Spine

With advancing age, the following degenerative changes are seen to occur in the spine:

Ligamentum flavum thickening,

Intervertebral disc degeneration,

Facet joint hypertrophy,

Reduced bone density,

Reduced vertebral body height,

Reduced intervertebral disc height,

Osteophyte formation.

Out of these changes, the first three are the commonest findings in LSS as these changes, alone or in conjunction with each other, lead to a reduction in the calibre of the spinal canal.

Ligamentum flavum thickening

This is noticed on most MRI scans in elderly patients. It is also noticed during surgery encroaching not only into the spinal canal but also out laterally into the neuroforamina. Ligamentum flavum thickening is a major contributing factor of LSS.^{viii} What causes this ligament to become thickened with age, whether it is hypertrophy or buckling, remains a matter of debate.^{ix,x}

It is well recognised that ligamentum flavum thickening increases with age. Park et al demonstrated on T1-weighted MRI, that the average thickness of the ligamentum flavum in the lumbar spinal canal of normal subjects with a mean age of 35 is 2.4mm whereas in LSS patients with a mean age of 62, the average thickness is 4.44mm.^{xi} Due to the fact that ligamentum flavum occupies a significant area of the posterior and postero-lateral wall of the spinal canal, an increased thickness of this ligament will result in a significant reduction of the volume of the spinal canal.

The ligament of young subjects is composed mostly of elastic fibres and only a few collagen fibres. With age, a degenerative cascade of events has been observed to occur and this ratio of elastin and collagen fibres is reversed. Several studies have reported pathological findings observed on histological sections of ligamentum flavum in

patients with LSS obtained either from lumbar surgery or post mortem. ^{xii,xiii,xiv,xv} Common findings in thickened ligaments were calcification, reduced elastin fibre to collagen ratio and fibrosis.

Various mediators have been postulated by several authors to be involved in the pathogenesis of ligamentum flavum thickening. Increased mRNA expression for transforming growth factor-beta 1 (TGF-beta1), GAPDH, lysophosphatidic acid and connective tissue growth factor has been observed on histological staining and immunohistochemistry. ^{xvi,xvii,xviii} These are hypothesised to be pro-fibrotic factors that have a role in the fibrosis observed in thickened ligaments.

The loss of elastic fibres is thought to cause the ligamentum flavum to buckle and some authors think that this is what aggravates the reduction in spinal canal volume, rather than simple hypertrophy of the ligament. ^{xix} Buckling of the ligament is a common finding on MRI scans of LSS patients. This also happens in part due to loss of intervertebral disc height which is also a common finding in the degenerative spine.

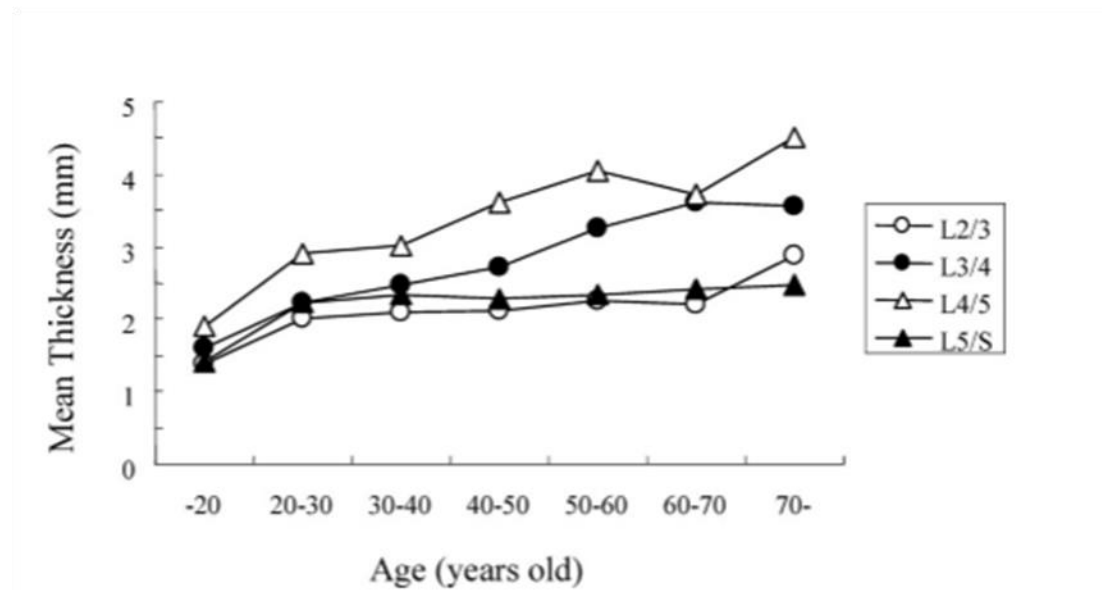


Figure 4 - The change in thickness of ligamentum flavum with age at each spinal level in the lumbar spine. From Sairyo et al. ^{xx}

What stimulates or sets off this degenerative process that leads to ligamentum flavum thickening has also been investigated. Other conditions are also associated with ligamentum thickening including disc degeneration and disc herniation ^{xxi} and high BMI. This means that it is not just aging and the passage of time that cause it. Biomechanical factors such as increased load and strain on ligamentum flavum can act as triggers to the fibrotic changes that lead to loss of elasticity and thickening. The ligamentum flavum at the lumbar spine is subject to more mechanical stresses than at any other level. Thickening of ligamentum flavum is seen to increase caudally with several studies reporting the L4/5 level as being the commonest level to have the greatest thickness. ^{xxii,xxiii} Reduction in disc height

has also been seen to be associated with increased thickening of ligamentum flavum and disc degeneration is also commonest at L4/5. This is in keeping with the increased mechanical stress experienced at this level. The clustering effect of these changes is likely to explain why LSS occurrence is also commonest at L4/5 level.

Intervertebral Disc Degeneration

With age the soft nucleus pulposus becomes less hydrated and more fibrous resulting in a reduction in the disc height. This contributes to the sagging seen in the elderly spine. This dehydration has been found to occur because of loss of the proteoglycans that fragment and leach out of the disc. The blood supply of the disc increases and the organisation of the collagen fibres within the annulus becomes disrupted and is lost over time. Like in the ligamentum flavum, an inflammatory cascade of events is seen to occur that leads eventually to structural failure of the disc.^{xxiv}

Loss of disc height impacts on other structures within the spine especially the facet joints. The biomechanics are altered resulting in increased strain on the joints even at physiological loads. It is well recognised that certain environmental factors and occupational hazards can accelerate the naturally occurring disc degeneration that occurs with age. Factors that cause inflammatory reactions such as smoking, microtrauma through heavy lifting and infection increase the risk of disc degeneration through activation of the degenerative cascade mentioned above. A hereditary influence has also been observed in twin studies.^{xxv} Degenerative disc disease is a major cause of low back pain. This is often referred to as discogenic pain and occurs when the symptoms of back pain arise in the absence of disc herniation. It is postulated that the inflammation within the degenerating disc acts as a nociceptive stimulus which causes pain through the sensory nerves that supply the disc. However, it has also been shown that as well as neovascularisation, degenerative discs also exhibit new innervation. This increase in nerve density makes the disc more sensitive to pain. In addition, degenerative discs also cause pain through herniation and compression of adjacent nerve roots leading to radiculopathy.

The intradiscal pressure in a healthy disc during physiological loads (approximately 700N during sitting) is highest in the nucleus pulposus and in the inner and middle annulus. Degenerative discs have a smaller nucleus and a wider annulus, as a result, there is higher stress on the posterior annulus especially due to the loss of hydrostatic pressure that imparts resistance to compressive loads.^{xxvi} Degenerating discs are a major contributor to the pathophysiology of LSS in several ways. Firstly, bulging or herniating disc occupy space within the canal. Also, loss of disc height contributes to sagging of the spinal column that contributes to buckling of the ligamentum flavum and the additional strain caused on the facet joints leads to hypertrophy of these joints over time. All of this resulting in stenosis of the spinal canal. Disc degeneration and age are intimately related but degenerative discs can also be found in young cadaveric spines implying that other factors are in play.

Facet Joint Hypertrophy

Osteoarthritis affects the lumbar facet joints just like any other synovial joint. The characteristics of facet joint osteoarthritis include joint space narrowing, osteophyte formation, articular process hypertrophy, sclerosis, subarticular erosion, subchondral cysts and vacuum phenomenon.^{xxvii} Enlargement of the joints through degeneration and/or osteoarthritis leads to spinal canal narrowing including the lateral recesses. Facet joint osteoarthritis and degenerative disc disease are commonly found together. This is because the paired facet joints and the intervertebral disc at each spinal level form what is known as the functional motion segment. Therefore, unsurprisingly, these structures are affected by similar mechanical factors. A relationship has also been observed between ligamentum thickening and facet joint orientation in the sagittal plane.^{xxviii} Heavy physical activity has been linked to accelerated degeneration of the facet joints, as well as increased BMI and advancing age.^{xxix}

In the lumbar spine, the facet joints occupy a small surface area compared to the size of the vertebral body end plate than they do in the cervical spine. In cadaveric studies, it has been estimated that at each spinal level these joints share on average 33% of the load, the rest being carried by the intervertebral disc. In the extended position, the applied compressive force on the discs is more than it is in neutral or the flexed position. With loss of disc height and narrowing of the intervertebral space, the pressure exerted on the facet joints is increased.^{xxx}

Histologically, the appearances of a similar degenerative cascade as seen in the intervertebral discs and ligamentum flavum is also observed in the facet joints which includes fibrosis, increased vascularisation and presence of inflammatory cells. In the early stages cartilage defects are seen in the joints especially at the periphery of the articular surfaces. Degenerative changes in the cartilage, such as fibrillation and flaking, can be seen even at a young age. Cartilage degeneration has also been noted to occur most severely at the L4/5 facet joints just like disc degeneration and ligamentum flavum thickening.^{xxxi} Attempts at healing these defects results in fibrosis. In addition, attempts at bone remodelling occur which lead to osteophyte formation. This is considered a sign of advanced joint degeneration.

Symptomatically, an arthritic facet joint can cause focal back pain due to innervation of the joint capsule from branches of the dorsal rami of the spinal nerves. Typically, this pain is located around the back and radiates down to the buttock but rarely goes below the knee. Radicular pain from nerve root involvement, however, can also occur in facet joint osteoarthritis. Increase in the size of the articular facets from hypertrophy and/or from joint swelling due to synovial inflammation, reduces the size not only of the central canal itself but also of the neuroforamen and can cause irritation and increased sensitivity of the traversing nerve root. Thus, symptoms of LSS can also arise from nerve root compression at the lateral recess and not just from thecal sac compression.

Epidemiology of Lumbar Spinal Stenosis

Lumbar spinal stenosis is especially common after the sixth decade of life since the condition is an accumulation of degenerative and age-related changes.

The epidemiological evidence of LSS relies only on a few studies and therefore only rough estimates can be calculated. (Table 1) One of the main difficulties in having an accurate calculation is that there is no agreed definite cut off size of canal diameter which defines LSS. The consensus definition of LSS is the presence of symptoms with radiological evidence of degenerative changes and reduced spine canal calibre. This is a subjective definition since the symptoms of LSS are heterogenous and patients often undergo surgical intervention which can skew epidemiological surveys that screen for symptoms. The following are the main studies who address epidemiology of LSS and low back pain.

Johnsson 1995, reported that the annual incidence of spinal stenosis observed in Sweden was approximately 5 per 100,000 inhabitants (45-59 per million). LSS was defined as a canal of 11 mm or less among patients referred to two major Swedish orthopaedic departments.^{xxxii}

The results of a cross-sectional study published in 2009, showed that the prevalence of degenerative mid-sagittal stenosis was 30% in the general American population (Framingham study).^{xxxiii} The same study also showed that radiographic stenosis was also common in asymptomatic individuals and absolute stenosis (sagittal diameter of <10 mm) had a threefold higher risk of associated back pain. Data extracted from the Framingham study showed that the prevalence of patients with LSS symptoms in the North American population is estimated to be 250,000-500,000.

In the National Low Back Pain study, the diagnosis of LSS was made in 14.0% of patients who were reported to have back pain.^{xxxiv} This was an American multicentre trial reporting the findings of a large heterogenous group of patients referred to Neurosurgeons and Orthopaedic surgeons.

The Wakayama Spine study is a population-based cohort study which included 938 Japanese participants (308 men and 630 women, mean age 67.3 years) that were selected from the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study. It is a cross sectional study where volunteers from the ROAD prospective database underwent whole spine MRI studies. In this study 30.4% of the participants were found to have severe central canal stenosis and out of these 17.5% were symptomatic. One third of the participants were found to have severe central canal stenosis of at least one level, with the commonest level being L4/5 and the prevalence of stenosis was found to increase with age (93% in age >80). A significant association of severe radiographic stenosis and presence of symptoms was demonstrated in this study.

Study	Country	Sample Size	Outcome
Johnsson 1995 ^{xxxv}	Sweden	163 (mean age 67 years)	Incidence of 50/year/million inhabitants
Long et al 1996 ^{xxxvi} Low back pain study	US	2,374 (mean age 45.3 years)	14% of patients with low back pain diagnosed with LSS
Kalichman et al 2009 ^{xxxvii} Framingham study	US	191 (mean age 52.6 years)	30% had radiographic stenosis
Ishimoto et al 2016 ^{xxxviii} Wakayama study	Japan	938 (mean age 67.3 years)	30.4% had radiographic stenosis of which 17.5% symptomatic

Table 1 - Summary of Epidemiological studies of LSS

The likelihood of LSS increasing with age has also been found in a study by Suri et al.^{xxxix} Patients younger than 60 were found to be much less likely to have symptomatic LSS than patients over the age of 70 (LR 0.4 vs 2.0).

There has been a dramatic rise in the incidence of LSS mostly due to the ageing population but also due to the ease of access to radiological investigations.^{xl} It is estimated that around 47% of patients older than 70 presenting to primary care with symptoms of pain or numbness in the leg have LSS.^{xli}

In the UK, there is sparse epidemiological data regarding the incidence and prevalence of LSS.^{xlii} Most epidemiological studies carried out are population surveys focusing on the prevalence of low back pain amongst people in the work force.^{xliii,xliv} In one study which formed part of the North Staffordshire Osteoarthritis Project, a postal survey was sent to 11,230 adults aged over 50 who were selected from three general practice registers. Out of the 7,878 respondents of the self-completed questionnaires, 56% were female and the average age was 66.3 years. The prevalence of low back pain by age group was 35.9% for 50-59 years, 35.1% for 60-69 years, 29.9% for 70-79 years and 27.3% for 80+. This shows an apparent decline in low back pain with increasing age, however the proportion of low back pain interfering with daily activities was 60.2% for 50-59 years, 67.2% for 60-69 years, 69.0% for 70-79 years and 78.2% for 80+. This decrease in prevalence of low back pain with increasing age is surprising given that low back pain is often associated with degenerative changes which worsen with age. Reasons for this could include increased pain tolerance with time or quiescence of the inflammatory changes as they become chronic. As expected though, symptom interference with quality of life did increase with increasing age.

Symptoms and Physical Examination

Many of the degenerative changes of the spine are asymptomatic. However, with time, as these changes accumulate patients often start to develop corresponding symptoms.

The symptoms of LSS are heterogenous but can be broadly divided into two main domains: Pain and Neuroischaemic domains, however high variability in the symptoms exists. In addition, the symptoms of LSS typically also have provocative and palliative features.^{xlv}

Pain

Back pain - can be nociceptive and/or neuropathic in nature. This is generally thought to arise from spinal structures other than the nerve roots. Inflammation of the facet joint from arthritis is a main contributor and this is often exacerbated by movement such as bending forward or backwards. Facet joint pain can radiate down to the buttocks and thighs, however rarely goes beyond the knees. Discogenic pain is also a major contributor of back pain. This is also seen in young adults with herniated discs and gives rise to deep seated back pain. The presence of back pain is not necessary to make the diagnosis of symptomatic LSS and is not considered as a classic LSS symptom. Symptoms of back pain are difficult to treat in LSS. This is because they are caused by irreversible degenerative changes and are usually multilevel and bilateral. Back pain by itself is rarely an indication for surgery unless an anatomically identifiable cause (e.g. tumour) is seen on imaging.

Radicular pain - arising from nerve root compression. This type of pain adopts a dermatomal distribution and can be unilateral or bilateral and is often asymmetrical. Pain from lower lumbar pathology tends to be below the knee (L4, L5 and S1 dermatomes) and from upper lumbar pathology the distribution is in the anterior thigh (L2 and L3 dermatomes). Surgery for radicular pain is often more successful than back pain. This is because root compression can be reversed by surgical bony decompression.

Neuroischaemic symptoms

The classic symptom of LSS is buttock or leg pain that comes on with walking and improves with rest and bending forward. Exertion worsens LSS symptoms and this is thought to be due to the inability to increase blood flow appropriately during exercise caused by the physical compression of the thecal sac. Neuromuscular symptoms including leg weakness, numbness and balance disturbance, are thought to be due to loss of proprioception resulting from nerve root compression.^{xlvi} Stucki et al found these symptoms to be highly prevalent in their spinal stenosis population of 193 patients. Two thirds report problems with balance, 77% reported numbness or tingling and 84% reported weakness.

The symptoms of LSS result in functional deficits especially in ambulation. Walking distance is often reduced in patients with spinal stenosis. This is thought to be due to the extended position of the spine during the upright

posture that reduces the calibre of the spinal canal. Limitation in walking has a major impact on quality of life and independence. The distance that can be achieved before symptoms start to occur tends to reduce over time. The absence of symptoms when seated and improvement when bending forward were found to be associated with the increased likelihood of having LSS in an elderly patient.^{xlvii}

Physical findings are uncommon. On examination patients may demonstrate an antalgic gait and have a reduced range of movement in forward flexion of the lumbar spine as well as extension. This is often due to facet joint arthritis. Nerve root tension sign on straight leg raising may be present. Specific neurological deficits such as loss of vibration sense and pin-prick sensation may also be found and may be in more than one dermatome. Objective weakness is not uncommonly present (29%)^{xlviii} as well as depressed patellar and ankle jerk reflexes.

The sensitivity of physical findings for the diagnosis of LSS is not high. A wide based gait and the provocation of anterior thigh pain with extension of the lumbar spine were found to be independently associated with a diagnosis of LSS.^{xlix} However these signs are non-specific.

Differential Diagnosis

Similar symptoms can be caused by the following conditions:

Vascular claudication – peripheral vascular disease can lead to ischaemia of the lower limbs. The sufferer may be pain free at rest however on exertion the increased oxygen demand of the lower limb muscles cannot be met by the reduced arterial circulation. As a result, the patient gets calf pain when walking a short distance, similar to the symptoms of LSS. Classically the difference between this type of claudicant leg pain and that of LSS is that the patient's symptoms are resolved simply by stopping whereas in spinal claudication the patient also needs to sit down or bend forward for alleviation of the symptoms. History, examination and investigations can help differentiate between LSS and vascular deficiency however it is possible that both can exist concurrently. In the history one must look out for vascular risk factors including smoking, diabetes and hypercholesterolaemia. The patient with identified peripheral vascular disease may have already been started on Aspirin and statin medication. On examination, it is important to confirm the presence of pedal pulses. If absent this should prompt further investigation. Tests to check the status of the peripheral circulation include ankle-brachial pressure index, Doppler ultrasound and digital subtraction angiography.

Peripheral neuropathy – Pathology affecting the peripheral nervous system can be caused by several conditions including Diabetes, Vitamin B12 deficiency, excessive alcohol consumption, drug induced such as chemotherapeutic agents or idiopathic. The symptoms of a peripheral neuropathy depend on whether just one nerve is affected (mononeuropathy) or multiple (polyneuropathy). The symptoms also depend on whether both

motor and sensory nerves are affected. In general, however the symptoms in the lower limbs are in a stocking distribution unlike those of LSS which tend to be dermatomal. Patient with peripheral neuropathy are more likely to have symptoms starting with their feet and may also, depending on the cause, have symptoms in their hands. Apart from history and examination the two conditions can be differentiated with electrophysiological tests including electromyography and nerve conduction studies.

Other Differential Diagnosis

Rheumatoid arthritis can also have similar symptoms to LSS such as stiffness and reduced mobility. This is an auto immune, chronic inflammatory disease of synovial joints which most commonly affects the metacarpophalangeal joints and cervical spine but any synovial joint can be involved including the facet joints of the lumbar spine. Rheumatoid arthritis causes deformity of the affected joints but is also often associated with a whole range of constitutional symptoms and extra articular disease that helps distinguish it from LSS such as fever, malaise, cutaneous, pulmonary and cardiac involvement.

Infective causes such as discitis or spinal osteomyelitis can result in severe low back pain which may also radiate to the lower limbs. Often these result in MRI changes that are identifiable, however chronic insidious processes may be elusive. Infection affects the spine most commonly via haematogenous spread, therefore a history of IV drug abuse or sepsis from other causes such as UTIs should be sought in the history. Iatrogenic causes such as spine surgery or injections can also result in infection through direct inoculation. In certain endemic areas, Tuberculosis should also be kept in mind.

Adult spinal deformity such as scoliosis can lead to similar symptoms of LSS. Scoliosis is an abnormal curvature of the spine in the coronal plane that often leads to back pain. Scoliosis can be congenital or adult onset. The acquired type has overlapping pathophysiology with LSS in that it is caused by degenerative changes of the spine. Imaging helps to distinguish this from LSS. The two conditions can overlap however and the presence of scoliosis needs to be addressed when deciding on the management of LSS.

Other pain syndromes such as musculoskeletal back pain also referred to as mechanical low back pain is thought to arise due to strain of paraspinal muscles and can co-exist with LSS. This is often diagnosed by exclusion of other causes.

Psychosocial issues may influence the symptomatology of LSS. Employment status, mental health, substance misuse and access to disability allowance can all be factors which play a role in the reporting of symptoms.¹

Natural History

Predicting the course of LSS has uncertainty. This is mainly because most patients receive some form of intervention to their spine and therefore the natural progression of the condition is not well known. The main

data regarding the natural history of LSS comes from the SPORT trial. Although this was a randomised control trial, the investigators also included an observational cohort who chose their own treatment. In total 235 patients with LSS were managed non-operatively. Out of these, 32% rated themselves as very or somewhat satisfied with their symptoms at 4 years. ^{li}

The British Association of Spine Surgeons gives a rough estimate that one in five patients improves with time, three out of five will remain with the same symptoms whilst the remaining one fifth will progress. The North American Spine Society's guidelines on degenerative LSS were unable to issue recommendations based on the evidence in the literature. In their consensus statement published in 2011 they estimate a favourable outcome in 35-50% of patients with symptomatic LSS who have minimal intervention.

As LSS is caused by degenerative changes, which tend to progress with the passage of time, it is most likely that symptoms of neurological compression will continue to deteriorate. However, since general mobility is also reduced with increasing age, the symptoms of neurogenic claudication may become less apparent giving the impression that there was a plateau or even an improvement in the symptoms. After surgical intervention to a single level, adjacent segments could also become stenotic leading to the patient developing symptoms again.

Management of Lumbar Spinal Stenosis

The goal of management of LSS is not to make the spinal canal wider but it is to alleviate the symptoms and improve the sufferer's quality of life. This is a challenging problem as, as described above, LSS is caused by several changes to the lumbar spine. There are several approaches to address the management of LSS and they can be broadly divided into operative and non-operative measures as described below.

Conservative Management (non-operative)

Conservative management refers to any treatment modality that can help alleviate the symptoms of spinal stenosis which does not involve surgery. Such management strategies do not directly reverse the narrowing of the spinal canal and do not alter the natural history of the disease; however, they can provide relief of symptoms and thus also have an impact on the patient's quality of life. Conservative management includes pharmacological therapy that can be administered as parenteral drugs or injected directly in the epidural space. Drugs include non-steroidal anti-inflammatory drugs (NSAIDs), opiates, antidepressants, muscle relaxants and anticonvulsants. Non-pharmacological therapy which mainly involves physical therapy such as physiotherapy, osteopathy and chiropractic are also offered for symptomatic relief. Often a combination of these options is offered.

There is no standard definition for conservative treatment and different modalities are applied by different practitioners. This makes comparative studies very difficult. There is little evidence in the literature to support any particular medical treatment. ^{lii} A Cochrane review found that epidural injections and physical therapy were supported by few low-quality studies. Despite this, conservative (non-operative) treatment is regarded as the first

line option offered to patients who are diagnosed with LSS. NSAIDs are the commonest group of drugs prescribed. Steroid injections in the epidural space or around the facet joints are also commonly offered prior to considering surgery. However, the literature reports that only a minority of LSS patients who are prescribed epidural steroid injections experience an improvement in symptoms that is enough to avoid surgery.^{liii}

The advantages of these non-operative options are that they are less invasive and repeatable. They also have a degree of placebo effect that is not insignificant.^{liv} Patients with LSS are often advised to persevere with multimodal non-operative treatment. This is especially the case when patients are not considered as appropriate surgical candidates or post operatively when symptoms persist despite surgery.

A multidisciplinary approach to pain management has been advocated as the best way to control symptoms non-operatively^{lv}. In the UK, it is common practice to advise patients to consult with a pain clinic where conservative management is explored by physicians who specialise in pain management and often undergo a trial of analgesia and injections prior to resorting to surgery.

Pharmacological Therapy

The role of drugs in LSS is mainly to address pain relief. However, controlling the symptoms of pain can also lead to improved mobility and function and reduced stress and anxiety. As mentioned earlier, LSS is a mixed pain syndrome which can include both nociceptive and neuropathic mechanisms of pain. The choice of analgesic drugs prescribed should therefore address the main type of pain that the patient describes and for this reason multiple agents with different mechanisms of action may be required.

NSAIDs are commonly used to manage nociceptive LSS symptoms and have been shown to be more effective than paracetamol in controlling back pain^{lvi}. The analgesic effect of this group of drugs is thought to occur due to the inhibition of prostaglandin synthesis by blocking the cyclo-oxygenase (COX) enzymes. NSAIDs also play a role in postoperative pain management however their prolonged use is not recommended due to adverse effects especially gastrointestinal side-effects.

Antidepressants are also frequently prescribed to address the neuropathic component of pain. Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as Duloxetine have been used with effective reduction in VAS scores of radicular pain.^{lvii} The analgesic effect of SNRIs is postulated to be separate to the anti-depressant effect.

Since neuropathic pain is different to nociceptive pain, neuromodulating drugs such as Gabapentin and Pregabalin are commonly prescribed to address the radicular symptoms of LSS which are neurogenic in nature. Gabapentin is an antiepileptic drug licenced for use in peripheral chronic neuropathic pain. A Cochrane review concludes that this drug reduces neuropathic pain from diabetic neuropathy in approximately 4 out of ten patients who use it, however more than half experience side effects.^{lviii} Pregabalin also has moderate benefit in most patients and

many will have no or trivial benefit.^{lix} Neither of these drugs are suitable for use in acute pain. The lack of substantial effect of these drugs is not surprising given the presence of ongoing mechanical compression of nerve roots from LSS. Hence why pharmacological therapy has a limited role in moderate to severe LSS.

Opioids have effects on both nociceptive and neuropathic pain pathways and are often prescribed when other drugs have failed to control symptoms. Tramadol is a dual-action analgesic with weak opioid μ -receptor affinity and was shown to be better than placebo for short-term relief of chronic back pain.^{lx} Stronger opioids such as morphine and oxycodone have shown mixed results with several trials reporting inconsistent results. This is likely to be due to the high incidence of side effects including nausea, vomiting, constipation and somnolence associated with chronic use. Markman *et al* failed to demonstrate clinical efficacy in the use of two common opioids (Oxymorphone hydrochloride and Propoxyphene) in the management of neurogenic claudication.^{lxi} In general, long term use of opioids is avoided in non-cancer pain.

Overall no class of drugs is clearly superior in obtaining pain relief of chronic low back pain and all are recommended only for short-term use. Duloxetine is the only drug with some evidence of significant effect however one should note that the trials that recommend its use are industry funded and therefore this could raise the possibility of bias in the interpretation of the analysis.

Non-surgical pharmacological interventions

Epidural administration of drugs such as steroids and local anaesthetics is a widely used non-surgical intervention in LSS. Huge controversy exists on the effectiveness of epidural and facet joint injections. In principal, the anti-inflammatory drug and/or anaesthetic agent are administered exactly at the site that is presumed to be the origin of the nociceptive stimulus, thereby bypassing the gastrointestinal system and the first pass effect of the liver. This, in theory, should cause fewer adverse events and the therapeutic effect should be more prolonged given the reduced systemic clearance. However, injections are an invasive procedure and the effects, even when successful, are short lived. They are often carried out with fluoroscopic or CT guidance to ensure appropriate administration especially for interlaminar injections. The indications for injections is often therapeutic but they are also commonly used for diagnostic purposes as well to help identify the source of pain. There is a wide variability in the way injections are administered. They can be given in different locations (facet joints, epidural space, nerve roots, intervertebral discs, ligaments etc.), different pharmacological agents (corticosteroids, NSAIDs, anaesthetics or combination) and different time intervals. Due to this source of variation in practice it is challenging to compare outcomes and analyse published data.^{lxii} It is also not uncommon for patients to report a variability in response to injections when repeated over time. In the literature, several trials have reported no significant difference between corticosteroid facet joint injections and placebo for the relief of back pain.^{lxiii, lxiv} One study suggests that the effect of peri-articular corticosteroids can be accentuated by combining it with lidocaine, however this only results in short term pain relief.^{lxv} Injections cost on average £600 in the UK compared to approximately £6,000 for

invasive decompression surgery. Although the cost is significantly lower and the risks of complications is far less than surgery, injections remain disappointingly unreliable and thus cannot be recommended as an effective treatment for LSS.

Non-pharmacological therapy

Many types of physical therapy exist including; exercise, physiotherapy, spine manipulation, massage therapy, superficial heat application, acupuncture, yoga as well as a range of psychological and cognitive-behavioural therapy. Several studies have been conducted and although the benefit and cost-effectiveness of each therapy is questionable, none seem to cause significant harm^{lxvi}.

Surgical Decompression

Laminectomy

LSS is the commonest indication for spine surgery.^{lxvii} Laminectomy is regarded as the gold standard surgical intervention for the treatment of LSS. It directly addresses the neurological compression by mechanically making the spinal canal wider. This is done by removing the lamina of the vertebra at the stenotic level thus creating more space for the thecal sac and the nerve roots within it. There are many variations of a lumbar laminectomy and it is mostly surgeon dependant. In a standard laminectomy the spinous process, the ligamentum flavum and the lamina on both sides at the stenotic level are removed. Often parts of the lamina of the vertebra above and below are also removed with undercutting of the facet joints. It is generally accepted amongst spine surgeons that up to two consecutive stenotic levels can be operated on without concern on affecting stability.^{lxviii} If more than two levels are decompressed, this risks causing instability which can exacerbate back pain and/or cause accelerated degeneration at the adjacent levels. To prevent this, instrumented fusion of the decompressed levels can be carried out to prevent motion and thus instability. Arthrodesis via spinal fusion is generally considered when two or more levels are being decompressed or when there is the presence of spondylolisthesis of Grade II or more on the Meyerding classification.

Laminectomies on the lumbar spine have been carried out since the 1850's.^{lxix} This operation provides access to the contents of the spinal canal and therefore it's indications are variable including decompression of the neural structures from hematomas or other collections such as pus and to treat spinal pathology such as tumours or vascular malformations.

Operative Procedure

Under general anaesthetic, the patient is positioned prone in a kneeling position with knees and hips flexed. It is crucial to ensure that the abdomen is free and not compressed to avoid venous engorgement and allow adequate ventilation. Equipment such as chest rolls or more commonly the Wilson supporting frame or Montreal mattress are used. (Fig. 5)

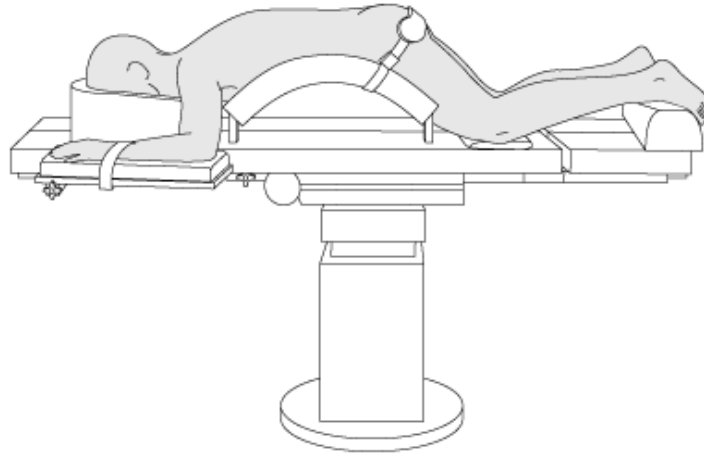


Figure 5 - Patient positioned prone on the Wilson supporting frame. Padding placed underneath pressure point, shoulders, elbows, knees and ankles. Head supported with a face mask. Reproduced with permission from AO Foundation.

The appropriate level is confirmed with X-ray guidance. A midline linear incision is made over the spinous process. The length of the incision depends on the number of levels planned to be decompressed. The spinous processes are exposed and the muscle is stripped away on one side if a unilateral approach is being used, or on both sides if a standard bilateral exposure is required. The lamina is then removed and the spinal canal is entered by removing ligamentum flavum. The extent of the spinous process osteotomy and laminectomy is surgeon dependent. Most surgeons aim to preserve the facet joints however at times the patient's anatomy precludes this. If there are short laminae or if the facet joints are prominent, adequate decompression may not be achieved unless a facetectomy is done. Undercutting of the facet joints is commonly carried out to enable decompression of the lateral recess. The microscope is commonly used for magnification and illumination after the initial approach. The superior-inferior extent and the lateral extent of the bony and soft tissue decompression are often determined with the appearance of the thecal sac and the ease of passage of an instrument such as a McDonald periosteal elevator. Haemostasis is ensured before closure and the dura inspected for any defects. A wound drain is often left in situ through a separate skin stab wound.



Figure 6 - Schematic diagram showing a top view of the spine after a standard laminectomy with removal of the spinous process and lamina bilaterally. From Boukebir et al^{lxx}

There are several approaches to decompress the spinal canal and the technique used is often a matter of surgeon's preference and experience but also dependent on the severity and extent of the stenosis being addressed. The classic standard open approach involves a bilateral muscle strip and removal of the entire posterior bony arch, including the spinous processes, for a wide decompression. (Fig. 6) In the last ten years however, there has been a trend towards minimally invasive bilateral decompression with preservation of the spinous processes together with the interspinous ligaments. Such microdecompression techniques via a unilateral approach and crossover seem to be gaining popularity amongst spine surgeons (the muscle is stripped from one side only and the spinous process is preserved but still performing a bilateral laminectomy). Several advantages have been reported including short operating times and less muscle trauma resulting in a quicker postoperative recovery.^{lxxi,lxxii} Hemilaminectomy of two adjoining levels is sometimes carried out if during the procedure, it is felt that the narrowing is mainly at the interlaminar level. Tubular retractors are used in some centres to minimise further the need for muscle dissection.^{lxxiii}

Due to this variance in techniques, the operative time of a laminectomy for LSS can range widely. Several factors influence the surgical time. These could be operator dependent such as the surgeon's experience or patient dependent such as the number of levels being operated on. On average operating times between 90 and 120 minutes have been reported by several trials.^{lxxiv,lxxv} The length of stay following surgery is around three days. In

some centres laminectomies are carried out as day cases however this is only done in selected patients and is not the norm in the UK. Both operating times and length of stay are significant direct costs of this procedure.

Complication Rate

A surgical complication can be defined as any event occurring as a result of an operative procedure that requires an intervention. Lumbar laminectomy is an invasive procedure with risks of significant complications. The mean overall complication rate is difficult to estimate due to differences in reporting outcomes, however from the literature this figure can be calculated to be approximately 9% and ranges from 1.7% to as high as 35%.^{lxxxvi,lxxxvii} In the SPORT trial (see below) the total complication rate in the LSS group was 12%.

Some studies conclude that the presence of co-morbidities rather than simply increasing age seems to be a more important risk factor for both systemic and wound complications.^{lxxxviii} A retrospective review of 471,215 patients, however, who underwent a lumbar laminectomy without fusion, in the US, between 1993 and 2002 found that the complication rate was highest in those aged over 85 and with the presence of three or more co-morbidities.^{lxxxix} With advancing age, the likelihood of co-existing illnesses increases and therefore it is difficult to quantify the independent effect of both factors. Given that LSS patients tend to be older, the risk of complications is higher than surgical decompressions for herniated intervertebral discs which tend to occur in patients under the age of 50.

Post-operative complications can be broadly classified according to the timing of their occurrence into early or late:

Early complications

One of the most commonly reported surgical complication following a decompressive laminectomy is a dural tear. The rate of dural tears has been reported to be as high as 9% in some studies.^{lxxx,xlxxxi} The resultant CSF leak from an inadvertent durotomy can lead to an increased length of stay, delayed wound healing and increased risk of wound infection. If recognised at the time of surgery a dural repair can be attempted. If presenting post operatively, additional procedures such as lumbar drain insertion or re-operation for CSF leak repair maybe necessary which further exacerbate the morbidity and inefficiency in cost.^{lxxxii}

Due to the removal of bone and stripping of muscle, blood loss can be significant during a laminectomy. The estimated average blood loss reported in the literature for a lumbar laminectomy is 100-300mls.^{lxxxiii,lxxxiv} An average drop in haemoglobin of 17g/L from pre-operative levels has also been reported.^{lxxxv} Despite this, the need for blood transfusion is uncommon. Bleeding, however, may persist after surgery and a postoperative haematoma has the potential to accumulate in the spinal canal and cause acute compression of the cauda equina requiring emergency evacuation. In a large retrospective review by Gordon et al, the incidence of post-operative haematomas was reported to be 5.2% (24,486 out of 471,215).^{lxxxvi}

Surgical site Infections can range from superficial wound infections to extensive epidural abscess and osteomyelitis, requiring re-do surgery for washouts and long term antibiotics. The estimated average overall infection rate is 5% with the risks being higher in the presence of a CSF leak and post-operative haematomas. Administration of prophylactic antibiotics at induction is standard practice in most centres and the application of intra-wound vancomycin powder is becoming widespread and has been associated with lowering the odds of infections.^{lxxxvii} *Staphylococcus aureus* and *Staphylococcus epidermidis* are the commonest offending microorganisms but resistant strains are emerging. Infection impedes wound healing and leads to scarring and can worsen pain symptoms thus interfering with clinical outcomes. It also increases hospital length of stay and direct medical costs of antibiotics.

Late Complications

Lumbar instability post laminectomy is a surgical complication that occurs after several months or years and can lead to failure of the decompressed motion segment. Spinal instability can be symptomatic causing back pain which is worse on movement. It is diagnosed radiologically as worsening spondylolisthesis (slippage of one vertebra on top of another) or spondylolysis on dynamic X-rays (lateral radiographs taken in flexion and extension positions).^{lxxxviii} Depending on the severity, arthrodesis of that segment may be indicated for symptom control but also to prevent neurological compromise. Predictors of instability after decompressive surgery include pre-existing spondylolisthesis, severe facet joint degeneration and disc degeneration as well as reduced bone density.^{lxxxix} Sparing the facet joints during a laminectomy is deemed important to prevent instability.

Chronic back pain following spine surgery, otherwise known as failed back surgery syndrome (FBSS) is an increasingly recognised complication. The condition is defined as back pain that persists despite adequate surgery when other complications such as infections have been ruled out. Although several mechanisms leading to FBSS have been postulated, such as epidural fibrosis and adhesive arachnoiditis, often no specific correctable reasons are found. Due to the non-specific aetiology, predictors of FBSS are unknown however some authors found that pre-existing depression or seeking work allowance may be risk factors. Treatments vary from pharmacological therapies to repeat surgery to implantation of spinal cord stimulators.^{xc}

Other complications

Procedures carried out in the prone position carry additional risks. There is increased thoracic compression in this position which affects cardio respiratory physiology. There is often a drop in blood pressure due to the resulting decreased central venous return. There is also reduced lung compliance due to increased peak pressures and increased intra-abdominal pressure. These effects can be reduced with supportive padding that allow the thorax and abdomen to hang free. Perioperative visual loss due to ischaemic optic neuropathy resulting from increased intra ocular pressure has been reported but is an uncommon occurrence (0.013% -1% of cases).

The morbidity associated with surgery can be more debilitating than the presenting symptoms. The occurrence of any complication increases costs and may lead to an increase length of hospital stay and delayed recovery. Furthermore, it could negatively affect long term outcome. It has been estimated that in the US, postoperative complications can increase the cost of non-oncological spine surgery by as much as \$121,366.^{xcii}

Outcomes and Cost Effectiveness of Laminectomy

Failure of symptom improvement is not a complication per se however it is an undesirable outcome for any invasive procedure and unfortunately it is not an uncommon occurrence in spine surgery. The success rate after a lumbar laminectomy for LSS is quoted to be around 70% in the literature^{xcii}. This data comes from two main trials comparing surgical decompression versus conservative management. The Maine Lumbar Spine Study and The Spine Patient Outcomes Research Trial (SPORT).

The Maine Lumbar Spine Study was a prospective observational cohort study which initially enrolled 148 patients. Out of this group 81 underwent surgery and initially 67 patients received conservative treatment. Patient rated outcome questionnaires showed that the surgical group had a greater improved outcome after one year compared to the non-surgical group even though the LSS on imaging was more severe (55% surgical vs 28% non-surgical).^{xciii} The authors then published the outcome after four years of follow up. From the original cohort, data was available in 67 operated patients and 52 patients who were managed non-surgically. Seventy percent of the surgical group reported an improvement in their main symptom after four years (event rate of 0.68) compared to 52% in the conservatively managed group (event rate of 0.51). This gives a number needed to treat of 5.8 ($1 / 0.68 - 0.51$). After ten years, 105 of the original 148 patients were alive. The overall outcomes were very similar between the two groups. Of these, 55% of the surgical group were satisfied with their status vs 49% in the non-surgical group. Better improvement of the predominant symptoms was reported by the surgical group (54% vs 42%). The cross over rate was 39%, meaning 22 patients of the original non-surgical group ended up having a laminectomy at some point over the ten years. In conclusion, the Maine study found initial improvement one year after laminectomy but similar outcomes long term to the conservatively managed group. Symptom improvement only slightly favoured the surgical group. The patients in this study were not randomised but chose whether to have surgery or not, thus the two groups are not strictly comparable. Also, the number of patients on whom follow up was available after ten years were only few in numbers.^{xciv}

The SPORT, on the other hand, was a randomised trial but also included an observational cohort. This was a five-year study that compared surgical decompression and conservative treatment for LSS, disc herniation and degenerative spondylolisthesis.^{xcv} The study concerning LSS randomised 289 patients to either surgery (138) or conservative treatment (151) and found that the surgical cohort had significantly better outcomes even after two years from surgery. The primary outcome measure was the SF36 and the surgical group showed a significant

improvement with a mean difference change from baseline of 7.8 for bodily pain. This improvement was also seen to be maintained at four years with mean treatment effect for bodily pain of 12.6 and for physical functioning of 8.6 .^{xcvi} In this trial, however, only 68% of patients randomised to surgery did actually undergo an operation. Also, out of those randomised to conservative treatment, 49% had undergone surgery by 4 years. The intention-to-treat analysis showed no difference between the operated and non-operated patients, however the as-treated outcomes showed a significant advantage of surgery.

Of note, both trials showed that a significant proportion of patients who did not have surgery reported improvement in their symptoms. In the Maine study, 28% of the non-surgical group reported an improvement after one year.

A meta-analysis of the literature in 1991 showed on average that 64% of surgically treated patients for lumbar spinal stenosis were reported to have good-to-excellent outcomes.^{xcvii}

A Cochrane review published in 2016 evaluated the effectiveness of surgery compared with various methods of non-operative interventions and concluded that there is not enough evidence to confirm whether surgical treatment or conservative management is better for LSS. A complication rate ranging from 10% to 24% was found in the surgical group versus none for conservative treatment.^{xcviii}

Another publication from the Cochrane library found no difference in outcome between different methods of surgical decompression such as unilateral laminectomy or split-spinous process laminotomy compared to conventional laminectomy.^{xcix}

The re-operation rate for spinal stenosis decompressive surgery after ten years is reported as ranging from 5-23%.^{c,ci,cii} An estimated 10% of re-operations have a fusion during their second operation. Reported re-operations for stenosis may not necessarily only include operations that are carried out at the same level that was operated on previously. Indications for re-operations are mainly recurrence of symptoms at different levels but also due to insufficient decompression at the same level.

Cost-effectiveness of Laminectomy

In the US it has been estimated that the cost to obtain an increment in the quality of life gained, at 2 years after surgery, is around \$77,600 relative to conservative therapy. This was calculated using the SPORT data.^{ciii} At four years this improved to \$42,800 per QALY gained. This means that the effect of surgery was sustained and therefore the cost is spread over more time. Direct costs for laminectomy were reported to range between \$12,615^{civ} and \$27,055^{cv}. In the UK, the cost of a laminectomy is estimated to be around £2000-£7000. Cost effectiveness and incremental cost ratios are discussed in Section 1.6. However, it is important to highlight that the way cost is

calculated differs in different countries and this will affect the cost-effectiveness of a procedure even if the clinical outcome is the same.

Interspinous Distractor Devices (IDDs)

Implantable interspinous distractor devices have been designed with the intention of widening the spinal canal and thus alleviating the compression on the thecal sac and vasculature. These devices were intended to preserve native structures and to be less invasive than the standard surgical decompression procedures that are commonly used to treat the symptoms of LSS. The first devices used were introduced into the market in the 1980's and became very popular amongst surgeons. They are also referred to as spacers and are inserted in between the spinous processes of two vertebrae. There are now several devices composed of different materials including titanium, PEEK and ceramics. IDD's are marketed for various indications either as implants on their own or as adjuncts to surgical decompression. It is controversial whether their efficacy and long term outcomes are better than the gold standard open approaches.

Biomechanics of IDD's in LSS

Due to the slumping and reduction in height of the intervertebral space that occurs in LSS as a result of the degenerative changes mentioned above, it has been postulated that distracting the spinous process can restore this loss of height thus increasing the calibre of the spinal canal as well as the height of the neuroforamina at the distracted level. Restoring height can also help unbuckle degenerative ligamentum flavum. As already mentioned, the calibre of the spinal canal varies with posture. In extension, the diameter of the canal is reduced and symptoms of LSS can be provoked in this way such as when walking or going down the stairs. IDD's stop this reduction by keeping the interspinous process space fixed even during extension.

There are several IDD's on the market which are used for LSS and several cadaveric studies have been carried out to study the effects of implanting IDD's on the biomechanics of the spine. Listed below are the IDD's used for LSS and their respective biomechanical studies:

X-Stop Interspinous Process Decompression System (Medtronic Spine LLC) - (X-Stop)

X-Stop was the first IDD to be approved by the U.S. Food and Drug Administration (FDA) in 2005 to be used in the management of LSS symptoms. It has been available in Europe since 2002. It was originally made out entirely of Titanium but one of the components, the spacer, was later changed to polyether ether ketone (PEEK). PEEK is a biomaterial as it has biomechanical properties that are more similar to human bone cortex than Titanium. It is a thermoplastic polymer and is widely used in implant materials. This device was designed to be inserted in between two spinous processes of the lumbar vertebrae thus keeping that segment of the spine in flexion but with minimal effect on motion other than limiting extension. It is composed of two lateral wings with a spacer in the middle. It

comes in two detachable parts. (Fig.7) The device is designed to pierce through the interspinous ligament and be in direct contact with the bone of the spinous process above and below at the implanted level. Once it is passed through the ligament and inserted in position, the detachable lateral wing is fixed to the spacer and the contralateral wing. The size of the spacer ranges from 6 - 14mm (6, 8, 10, 12 and 14).

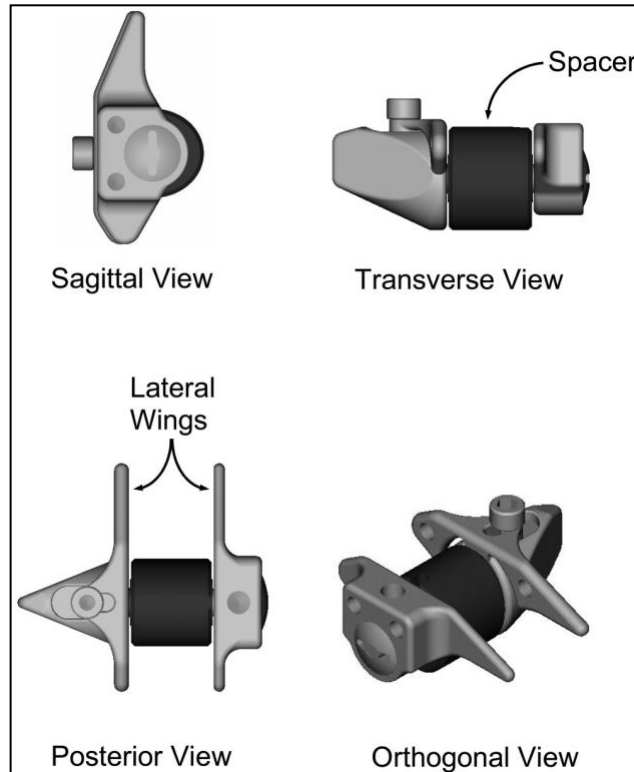


Figure 7 - Schematic representation of the X-Stop Implant (Medtronic Spine LLC) taken from Richards et al, 2005.^{cvi}

Operative Procedure

The procedure is carried out with the patient's spine flexed, this can be in either the prone position or in the lateral decubitus position. A midline linear longitudinal skin incision about 5-8cm long, depending on how many levels are going to be treated, is carried out after the appropriate operative level(s) is confirmed with X-rays. Longitudinal dissection of the muscle is done on either side to expose the two spinous processes down to their base whilst preserving the interspinous ligament. A dilator is then used to pierce the interspinous ligament as close to the lamina as possible. The dilator is also used to distract the spinous processes apart. A gauge is then inserted to measure the appropriate size of the device. Fluoroscopic guidance can be used at this stage to ensure that the gauge is as close to the spino-laminar junction as possible. The appropriately sized device is opened and loaded on the inserter. The spacer part of the device is passed through the defect in the interspinous space and deployed from the inserter which is then withdrawn. The detachable wing of the contralateral side is then loaded and inserted on the opposite side and mounted on the spacer then secured in. Final X-rays can be done to ensure

correct positioning. It is important that the correct size is selected which gives some distraction to the posterior elements without breaking the spinous processes.

In theory, this procedure can be carried out under local anaesthetic however in the event of spinous process breakage the procedure could be converted to a laminectomy in the same sitting (with prior consent from the patient) and therefore a general anaesthetic would be required. Also, manipulation of the spinal muscles to expose the spinous processes can be uncomfortable and an overall traumatic experience for the patient.

Biomechanics of the X-Stop IDD

Effects on canal dimensions: In one cadaveric study, the investigators measured the spinal canal area and diameter, subarticular area, neuroforaminal area, height and width as well as ligamentum flavum thickness of eight cadaveric spines at L2/3, L3/4 and L4/5 in three different positions; neutral, 15 degrees of flexion and 15 degrees of extension. They then implanted the X-stop device at the L3/4 level and carried out the same measurements. These measurements were taken using a 1.5 Tesla MRI scanner.^{cvi} They demonstrated that, as already known, the mean canal area and diameter are reduced in extension in the intact spine (area in flexion 286mm² vs 231mm² in extension). With the X-stop device however both the canal area and diameter at the implanted level were increased during extension (area in flexion 276mm² vs 275mm² in extension). This amounts to an average of 18% increase in the canal area in extension and 6% in neutral position with no significant difference in flexion. The same increase in the extended position at the implanted level was seen for the rest of the parameters: the canal diameter increased by 10%, the subarticular space increased by 50%, foraminal area by 25% and foraminal width by 41%. Foraminal height did not change significantly. Ligamentum flavum thickness also did not vary between intact and implanted spines. There was no significant difference in any of the measurements in the adjacent levels. This is a significant finding since one of the major drawbacks in surgical decompression is the increased load on the adjacent segments of the decompressed level and the consequential acceleration of degeneration.

Hirsch et al also demonstrated an increase in neuroforaminal height at the implanted level with no effect of the adjacent level in extension. Six cadaveric spines were implanted with several IDD's including the X-Stop at the L4/5 level. The group reports that with the X-Stop device the increase in neuroforaminal height was found not only in extension but also in the flexed and neutral position.^{cvi}

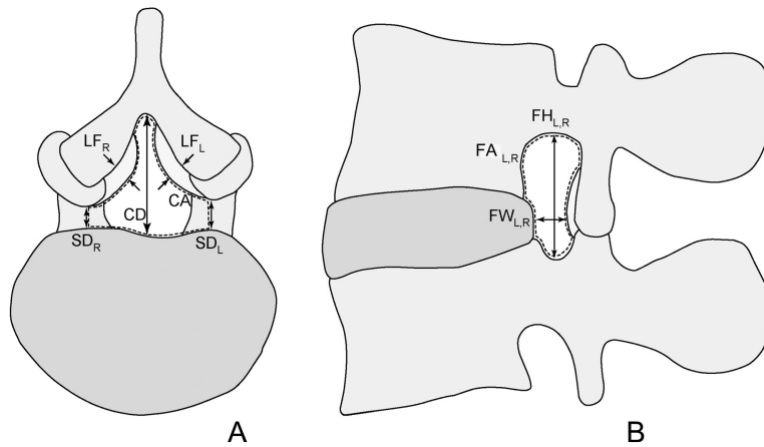


Figure 8- A schematic representation of axial and sagittal slices in the pedicular plane. CA - canal area, CD - canal diameter, FA - foraminal area, FH - foraminal height, FW - foraminal width, LF - ligamentum flavum, SD - subarticular diameter. from Richards et al.

Effects on intervertebral discs: Other cadaveric studies on the X-Stop IDD have shown a reduction in intradiscal pressure in extension but not in flexion and not in adjacent discs.^{cxix,cx} Swanson et al implanted the X-stop at the L3/4 level in eight cadaveric lumbar spines (L2-L5) aged between 56 and 80 years. Using a very thin pressure transducer, the intradiscal pressure was measured at all levels, L2/3, L3/4 and L4/5. A compressive force of 700N was applied in the neutral, flexed and extensor position. The authors report that a significant reduction in intradiscal pressure was found in both the posterior annulus and in the nucleus in the extended and the neutral position at the L3/4 level. In addition, there was also a reduction in the pressure measured in the anterior annulus in the flexed position. No significant differences were found in the adjacent levels except for a reduction in the L4/5 nucleus pressure in flexion.

Effects on facet joints: As mentioned previously the load on the facet joints is increased in the extended position. In degenerative joints this can result in compression of the nerve roots. Wiseman et al studied the effect of the implant on the lumbar facet joints of seven cadaveric spines by applying a 700N compressive axial load and measuring the pressure in the joint space using a pressure sensitive film.^{cxii} The device was implanted at the L3/4 level and measurements taken before and after implantation at L2/3, L3/4 and L4/5 levels bilaterally. The investigators demonstrated that the peak pressure on the facet joints at the implanted level was significantly reduced by 55% and the mean pressure reduced by 39%. No significant changes in pressure were noted in the adjacent facet joints. (Fig.9)

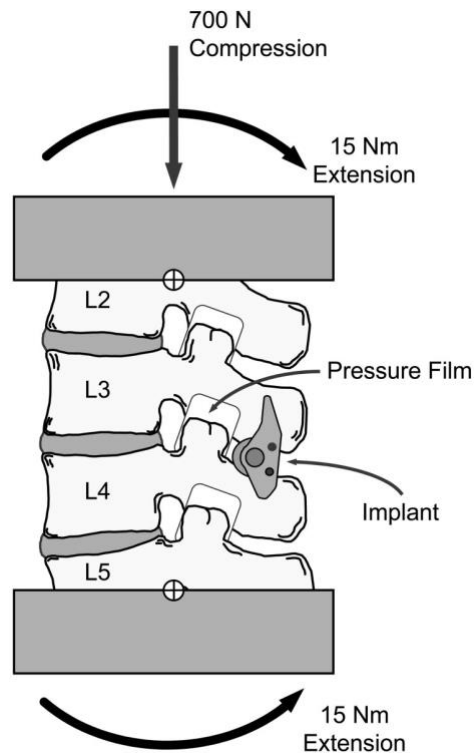


Figure 9 - A schematic of the testing configuration. A 15 Nm bending moment was applied to each specimen via servohydraulic rotational actuators secured to the cranial and caudal ends of the specimen, and a 700 N axial load as applied via a servohydraulic linear actuator at the cranial end. The cross-hairs represent the centres of rotation for the cranial and caudal rotational actuators. from Wiseman et al^{cxii}.

Clinical Evidence of Efficacy of the X-Stop IDD

X-Stop Vs conservative treatment

Anderson and colleagues randomised 75 patients to either X-Stop implantation or conservative management and completed two-year follow up in 70 of these patients.^{cxiii} Conservative treatment consisted of NSAIDs, analgesia and at least one epidural steroid injection. The X-Stop group (42 patients) had statistically significant improvement in both the Zurich Claudication Questionnaire (ZCQ) (15-point improvement) and SF36 scores for all time points. Five patients in the X-Stop group and four in the conservative group eventually had a laminectomy. Clinical success was defined as an improvement of 15 points of the ZCQ from baseline, a patient satisfaction score of less than 2.5 on the SF36 and no re-operations. Overall, after two years, 12.9% of patients in the control group Vs 63.4% in the X-Stop group were considered to have been clinically successful.

Zucherman et al were the first group to carry out clinical studies using the X-Stop. 191 patients were randomised to either X-Stop insertion or conservative treatment (control group) and were followed up for four years. The first

publication reported the outcomes after one year of implantation of the device.^{cxiv} They reported outcomes using ZCQ and SF36 questionnaires. At each time point (6 weeks, 6 months and one year) the X-Stop patients were significantly more pain free, had significantly more improved function and were more satisfied than the non-operated group who showed no significant improvement from baseline. In the publication reporting the two-year outcomes, the authors again reported significant improvement with the X-Stop at every time point using the ZCQ as their outcome measure.^{cxv} At two years the data available for follow up was from 93 of the original 100 X-Stop patients and from 81 of the 91 patients in the control group. The overall improvement in the symptom severity score of the ZCQ was 45.4% in the X-Stop group and 7.4% in the control group. The improvement in the mean physical function score improved by 44.3% vs a deterioration of -0.4% in the control group. The incidence of re-operation was 6% in the X-stop group. The authors report the outcomes of the SF36 questionnaires in a separate publication that focuses on quality of life.^{cxvi} Out of the 82 X-stop patients on whom SF36 data was available, 6 underwent laminectomy. Out of the 53 conservatively managed patients, 24 eventually underwent a laminectomy. The authors report both their intention-to-treat analysis as well as as-treated data. The X-stop group showed significantly better scores in most domains at all time points except for the general health domain, role emotional and the mental component summary at 2 years. As expected it is the physical functional domains that improved significantly. On the other hand, the conservative group had no significant difference in any domain at any time point post operatively.

X-Stop Vs conventional surgery

Evidence in this area now includes four randomised control trials (RCT's). Three RCT's; Stromqvist et al 2013, Moojen et al 2013 and Lonne et al 2015, investigated the use of the X-stop versus standard decompression.^{cxvii,cxviii,cxix} Azzazi et al 2010 randomised the X-stop Vs Surgical decompression and fusion.^{cxx}

Stromqvist et al randomised 50 patients for surgical decompression and 50 patients for X-stop insertion. They found no significant difference in the primary outcome (improvement on Zurich Claudication Questionnaire, ZCQ) but a higher re-operation rate in the X-stop group (26% vs 6% $p=0.04$). These patents were followed up for twelve months.

Moojen et al recruited 159 patients from five centres in the Netherlands and had a follow up of twelve months with the primary outcome measure also being the ZCQ. They found similar findings to the Swedish group; no significant difference in outcome between the two groups except for the high re-operation rate of the X-stop patients (29% vs 8%). The advantage of this study was that it was a double blinded study and neither the patients themselves nor the investigators collecting the post-operative data were aware of which operation was carried out.

The Norwegian study by Lonne et al is slightly more controversial as it was stopped early after the interim analysis showed that the X-Stop arm of the study was substantially more expensive than minimally invasive decompression. Ninety-six patients were randomised to either X-stop insertion or to a limited laminectomy where the spinal canal was opened but only the inferior aspect of the lamina and medial part of the facet joints are decompressed. Full cost data is only available for 81 patients since the study was terminated early. The re-operation rate in the X-Stop group was 30% (13 patients out of 41) Vs 12% in the minimally invasive surgical group. The high rate of secondary surgery together with the initial cost of the implant led to the study being stopped early as the cost-effectiveness was not in favour of the device.

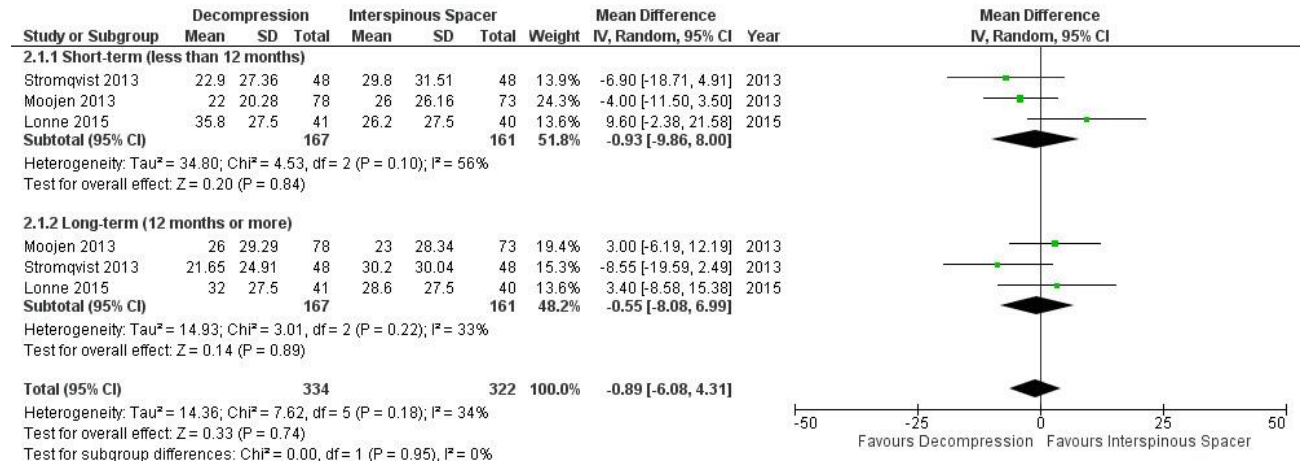
Azzazi and Elhawary compared transpedicular screw fixation to the X-stop for management of LSS. They randomly assigned 60 patients to one of the two arms and found the X-Stop device to be preferable to fusion. In the X-Stop arm the Oswestry Disability Index (ODI) score improved from 53% to 26.5% whereas in the surgical fusion group the ODI improved from 55% to 34.5%. Moreover, the transpedicular screw fixation arm had more significant complications than the IDD group including screw loosening in two cases and three dural tears with an overall complication rate of 14/30 vs 3/30. The length of stay was one day for all the X-Stop cases compared to three days in the fusion group. The average operating time was three times as long (45 minutes for single level X-Stop vs 150 minutes for transpedicular screws).

Other devices

Davis et al investigated the Coflex device and randomised patients to decompression and Coflex or laminectomy and fusion.^{cxix} Therefore this was not a trial looking at an IDD as a standalone device but as an adjunct to standard surgical decompression.

A summary of all the clinical evidence regarding all the various IDDs and how they compare with other conventional surgical options can be found in a recent Cochrane review on the surgical treatment of LSS published in 2016.^{cxix} This included 24 randomised control studies with 2352 participants with LSS and claudicant symptoms. Only five out of these trials investigated the effects of IDD's. The review showed that interspinous devices were slightly superior to decompression with fusion in controlling pain. However, compared to decompression alone, although IDD's had similar rates of pain control, they had higher re-operation rates. (*Fig. 10*)

A Decompression Vs IDD



B Decompression with fusion Vs IDD

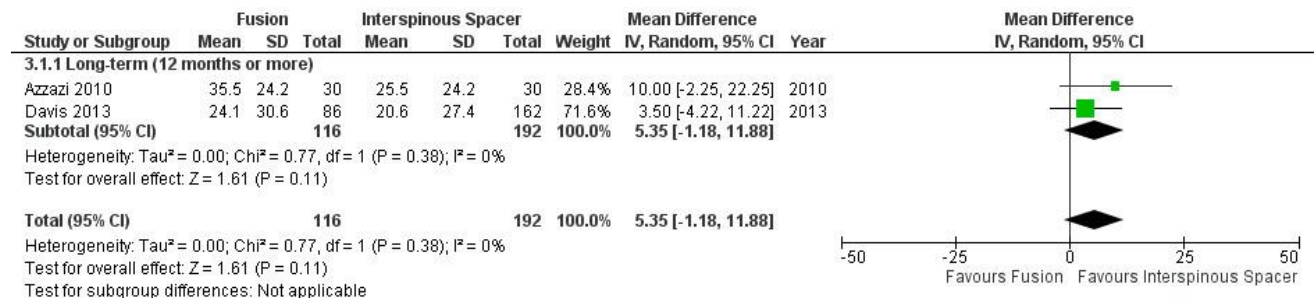


Figure 10 - Forest plot of comparison: A) Decompression versus interspinous spacer. B) Decompression plus fusion versus interspinous spacer. Cochrane Library Cochrane Database Syst Rev. 2016 Nov 1;11:CD012421

Clinical Guidelines

NICE Guidelines

The National Institute for clinical excellence has updated its guidance in 2010 with regards to the management of LSS. Surgery in the form of decompression or fusion is only recommended in LSS where the symptoms are refractory to analgesia. NICE recommends that the use of IDD's in this condition is safe and efficacious in the short and medium term in carefully selected patients. The guidance is based on an RCT of 191 patients (Zucherman et al), 3 non-randomised control studies, 7 case series and 2 case reports. The full guidance can be accessed through the institution's website at: <https://www.nice.org.uk/guidance/IPG365/chapter/1-guidance>.

North American Spine Society Guidelines

The NASS concludes that surgical decompression improves outcomes in moderate and severe LSS and grades this recommendation as grade B meaning that based on studies published in the literature the society suggests the use of intervention (Grade A recommends its use, B – suggests, C- indicates and I – insufficient evidence). For the use of IDD, the NASS states that there is insufficient evidence to make a recommendation for or against. This guidance is available at: <https://www.spine.org/Documents/ResearchClinicalCare/Guidelines/LumbarStenosis.pdf>

Outcome measures

Definition

Outcome measures are assessment methods used to objectively find out the effect of an intervention. In the medical field, they are a standardised way to compare different subjects and different interventions. Outcome measures serve as tools that generate a reproducible result, which minimises investigator bias.

In addition to assessing treatment outcome, these tools can be used to monitor progress, make a diagnosis as well as screening. In healthcare, outcome measures are often used to measure cost-effectiveness, compare different providers and improve quality of care.

Various tools can be used to measure the outcome after an intervention such as radiological tests before and after a procedure or a drug administration. In the clinical setting however, where the objective of a treatment procedure is to improve patients' symptoms, having a good radiological outcome might not necessarily result in a perceived good outcome by the patients themselves. For this reason, Patient Reported Outcome Measures (PROMS) are now utilised more frequently since they provide patient focussed assessment.

Cost of treatment is another form of assessing outcome by determining efficiency. Comparing the cost of different treatments for a condition can help identify potential savings for the healthcare provider. Cost effectiveness, however, is determined not only by the direct costs of providing a service, such as the price of a device, but also on indirect measures such as quicker return to work.

Patient Reported Outcome Measures (PROMS)

PROMS provide a standardised scoring system for carefully selected questions. These tools have been shown to improve patient satisfaction with care and are routinely used in spine surgery and in clinical trials.^{cxiii} PROMS can be classified in to two main categories; disease specific, where the patient reports outcomes specific to the condition being managed or a particular intervention received, and general health PROMS which are used in a broader way to assess the general wellbeing and psychosocial status of an individual, which can in turn have an impact on their perception of treatment. It is well recognised that coexisting illnesses may act as a burden to

ambulation and recovery from surgery and should be taken into account when considering the outcome of an intervention. Disease specific PROMS are very sensitive to the condition being managed but they offer only a narrow assessment of health. These types of PROMS are not very useful to estimate quality of life like generic PROMS, for this reason good clinical trials often use both types to obtain a comprehensive result.

When using PROMS in a study one must consider the following; validity, reliability, sensitivity and feasibility. This means that an instrument which is being used to measure outcome needs to be accurate and repeatable, i.e. it consistently obtains the same result. It also needs to be able to detect clinically important changes but it also needs to be easy to use and appropriate for the population being studied. There are inherent problems of subjectivity with collecting data directly from patients. Patients may answer differently from day to day even if their health state or condition hasn't changed. Also, there might be changes from day to day to their status for instance pain severity can fluctuate. This is called intra patient variation and the accuracy of the data might suffer because of this.

General health and Quality-of-life PROMS

These questionnaires are not condition-specific and therefore can be used to assess the outcome across various populations, not just in people suffering with the same condition. They allow comparisons of general health as perceived by patients themselves. Examples include; European Quality of Life (EQ-5D), The Nottingham Health Profile, Short Form survey (SF-36) and Health Utilities Index (HUI). Although they provide a comprehensive outlook on life they can be long and tedious and not very sensitive to some problems. These generic quality of life PROMS can be further subdivided into profile or index measures. The aim of profile PROMS, like SF-36 for instance, is to provide a profile of an individual's health. They often have different categories within the questionnaire and the result is not simply just one figure. Index measures on the other hand, such as EQ-5D, aim to provide a simple index value to represent an individual's health. Profile and index measures therefore have a different valuation burden (EQ-5D has 243 possible health state permutations / SF-36 has 18,000 possible permutations).

The EQ-5D and SF36 are the most widely used quality of life measures as one can also use these tools to estimate QALYs (see below).^{cxxiv}

EQ-5D

The EQ-5D is one of the most widely used patient surveys in clinical trials. It is generated by the EuroQol group. It is a standardised questionnaire that has been designed for self-completion and aims to measure health status in a simplified way. EQ-5D was introduced in 1990 and has five dimensions; Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. There are two versions of the questionnaire; 'EQ-5D-3L' and 'EQ-5D-5L' where each dimension has either three answer choices or five, respectively. The original version of the survey had

three levels of response for each dimension: no problems, some problems and extreme problems. In 2005, the 5L version was introduced where there are an additional two levels of severity: no problems, slight problems, moderate problems, severe problems and extreme problems. The use of EQ-5D as a patient rated outcome measure is advised by NICE and is also part of the NHS PROMS programme.^{cxxv}

The EQ-5D consists of two pages: one is the descriptive system and the other is the visual analogue scale (VAS). In the first page the respondent is asked to indicate with a mark, for all the five dimensions, which of the choices reflects most appropriately their current status. In the EQ-VAS section the user is asked to indicate their self-rated health status on a vertical linear scale labelled 'Best imaginable health state' at one end and 'Worst imaginable health state' at the other.^{cxxvi} (Appendix)

This tool for outcome measurement has been used for a wide range of health applications. It has the advantage of being simple and less time consuming therefore facilitating data collection. The choice of response by each patient is referred to as their health state. With three possible answers for each of the five dimensions there are therefore a total of 243 possible health state combinations. Each level is indicated by a number (1– no problems, 2- some problems and 3- severe problems). Each health state is recorded as a five-digit code based on the number of level chosen for each response. For example, if a patient has no problems in each of the five dimensions, the code for their health state is 11111. A health state of 33333 implies severe restrictions in all dimensions of health. Missing values are recorded as 9. The EQ-VAS is recorded as a whole number based on a scale of 0 to 100. Missing values are recorded as 999. A Time trade off (TTO) score is calculated for each health status so that a health index ranging from -0.594 (UK) to 1.00 can be given. Full health i.e. a score of 11111 gives a TTO score of 1.00.

The way that a patient responds to the EQ-5D can be influenced by their socioeconomic status. For this reason, a valuation technique to account for this societal perspective can be applied. These population norms have been collected for several countries including the UK.^{cxxvii}

SF36

The 36-item short form health survey (SF36) was developed by the RAND organisation as part of the Medical Outcomes Study. It is a quality-of-life questionnaire that was developed as a PROM. It assesses general health by addressing basic concepts such as functioning and emotional well-being. It consists of a series of questions that represent eight aspects of health; physical, social and role functioning, mental health, general health perception, bodily pain, emotional functioning and vitality (energy/fatigue).^{cxxviii}

The questions were carefully selected using psychometric standards and data from previously used full-length surveys. (Table 2)

Concepts	No. of items	No. of levels	Meaning of scores	
			Low	High
Physical functioning	10	21	Limited a lot in performing physical activities including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role limitations due to physical problems	4	5	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health, past 4 weeks
Social functioning	2	9	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems, past 4 week
Bodily pain	2	11	severe and extremely limiting pain	No pain or limitations due to pain, past 4 weeks
General mental health	5	26	Feelings of nervousness and depression	Feels all of the peaceful,

				time	happy, and calm all of the time, past 4 weeks
Role limitations due to emotional problems	3	4		Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems, past 4 weeks
Vitality	4	21		Feels tired and worn out all the time	Feels full of pep and energy all of the time
General health perceptions	5	21		Believes personal health is poor and likely to get worse	Believes personal health is excellent

Table 2 - Interpretation of SF36 questions and breakdown of scores.

The SF-36 is a multi-item linear scale and its analysis and interpretation assumes that the scores are linearly related to the aspects of health being measured. Each item on the survey carries a score. A higher score indicates a more favourable outcome and the resultant score is a percentage of the maximum score possible. Items that are left blank are not counted therefore the final score is only a percentage of the questions answered.^{cxxix,cxxx,cxxxi,cxxxii}

In general, the domains of physical functioning, role limitations due to physical problems and bodily pain pertain mostly to physical health whereas the rest of the five domains are grouped as mental health measures. Therefore, although the SF36 can be used across various diseases and conditions, the domains that are most sensitive to change can differ depending on the disease or condition that the tool is being used for. For instance, in LSS one would expect the physical health score domains to change after treatment as mental health is unlikely to be significantly impacted on by undergoing surgery.

The SF36 health survey was not originally designed to be used for economic evaluations of health or to determine QALYs. However, Professor Brazier from Sheffield University has devised a scoring method to obtain a health utility

index using seven out of the eight domains (the general health domain is not used). The two domains of role physical and role emotional are combined, resulting in six domains. The score is therefore referred to as the SF6D index. The resulting score can range from zero (worst health state) to 1 (full health).^{cxxxiii}

Disease-Specific Outcome Measures

Zurich Claudication Questionnaire (ZCQ)

ZCQ is a self-reported questionnaire which addresses symptoms of LSS. It is divided into three scales: symptom severity, physical function and patient satisfaction. The questionnaire was developed in 1996 by Stucki et al as part of a prospective, multicentre, observational study on patients with LSS undergoing decompressive surgery. ZCQ has a good test-retest reliability which makes it reproducible and consistent. It consists of a total of eighteen questions; seven in the symptom severity scale, six questions addressing physical function and five assessing satisfaction with surgery. The latter section can only be filled out post-operatively. Two domains are assessed in the symptom severity scale; three components address the pain domain and four represent the neuroischaemic domain (leg pain, weakness, numbness and balance disturbance).^{cxxxiv}

Pratt et al concluded that the ZCQ was the best outcome measure for LSS patients.^{cxxxv} They tested the ODI, ZCQ, Oxford claudication score and the walking test and the repeat test reliability of each in patients with LSS.

A 15-point improvement in scoring the ZCQ is considered as clinically significant. (Appendix)

Oswestry Disability Index (ODI)

The ODI is one of the most commonly used self-administered questionnaires to assess back pain. It consists of ten questions each of which assesses the impact of back pain on an activity of daily living. For each section the score ranges between zero and five, with zero being no symptom interference and five being unable to perform an activity due to the symptoms. The total score is expressed as a percentage of the possible total score (50). If one section is left out 5 points are deducted from the possible score. (Appendix)

Quebec Back Pain Disability Scale (QBPDS)

This questionnaire is based on twenty items that aim to assess the effect of back pain on functionality. The QBPDS has been shown to be reliable valid and repeatable and is commonly used in clinical trials to monitor progress.^{cxxxvi} Disability is defined by the WHO as “any restriction or lack of ability to perform an activity in a manner or within the range considered normal for a human being”. The QBPDS was developed with this in mind and therefore its

questions are directed at the ability of a person to perform certain tasks and the difficulty that that person finds in doing them. The twenty activities can be grouped into 6 categories; at rest, sitting, ambulation, moving objects, bending and handling large objects. A five point Likert scale is used for each question with zero for no difficulty and 5 for being unable to perform the task. The maximum score is 100% and the higher the score the greater the level of disability. This instrument can be used for any condition where back pain plays a role including LSS, disc degeneration, acute back pain or sacroiliac joint dysfunction. (Appendix)

Cost- Effectiveness

Cost is another metric of outcome and is an important factor when it comes to decision making and delivering excellent quality of care. Cost-effectiveness however, is the best means of assessing the economic evaluation of an intervention. This is because it takes into account the cost of, as well as the clinical benefit that the treatment had on a patient. The more costly a treatment or intervention is, the less cost-effective it becomes and the less clinical benefit obtained from a procedure the less the cost-effectiveness. (Fig. 11) The unit used for cost-effectiveness is cost per quality-adjusted life-year (QALY) gained. Or more simply put, health gain per every '£' spent of public health care resources. QALYs are a widely used and popular method of representing cost-effectiveness and are also used by NICE to advice on new drugs, therapies and services.^{cxxxvii} It was first introduced in the 1970's as a health index however it only became a reference standard in healthcare economic evaluations in the 1990's. ^{cxxxviii} Disability-adjusted life year (DALY) evolved from QALY. DALY represents the burden of disease and also takes into account loss of function from a disease or condition as well as puts weighting on age in its calculation. Both QALY and DALY are types of non-fatal health outcomes which measure health in time (life years) in a population and can be used as comparative indicators of an intervention. Other measures such as morbidity and mortality are also frequently used however these would not provide the necessary detail in comparing treatments in chronic diseases such as LSS.^{cxxxix}

Choice based quality of life questionnaires such as EQ5D and SF36 can be used to calculate QALYs, whereas disease specific questionnaires are not very helpful in this regard as although they are sensitive to the particular condition, they cannot be compared across different conditions. Various methods exist to calculate QALY but all are based on the following simple formula:

$$QALY = (Length\ of\ life) \times (Quality\ of\ life)$$

or $T \times U$

where U is the utility used to measure quality of life, for instance the EQ5D TTO score, multiplied by time (T) from the intervention taking place measured in life years. QALY gives you the health state measured in cardinal values where 1 is equal to perfect health and the value of 0 is death. Life years can be obtained from official published life expectancy statistics. In the UK these are obtained from the office for national statistics. QALYs can be represented on a graph where the independent variable is time and the dependent variable is quality of life on the Y axis which ranges from 0.1 to 1. Three main methods of QALY calculation have been described by Manca et al.; The 'area under the curve' calculation, 'change from baseline' and the 'regression' method.^{cxl} When using the 'area under the curve' method, the average EQ-5D value over the whole study period is used. For the 'change in baseline' method the difference between the EQ-5D value at the end of the study period from the value before the intervention is averaged out over the whole study duration. The 'regression' method accounts for differences at baseline between the groups being compared, then uses the area under the curve method. It is therefore an intermediate method of the previous two. ^{cxlii}

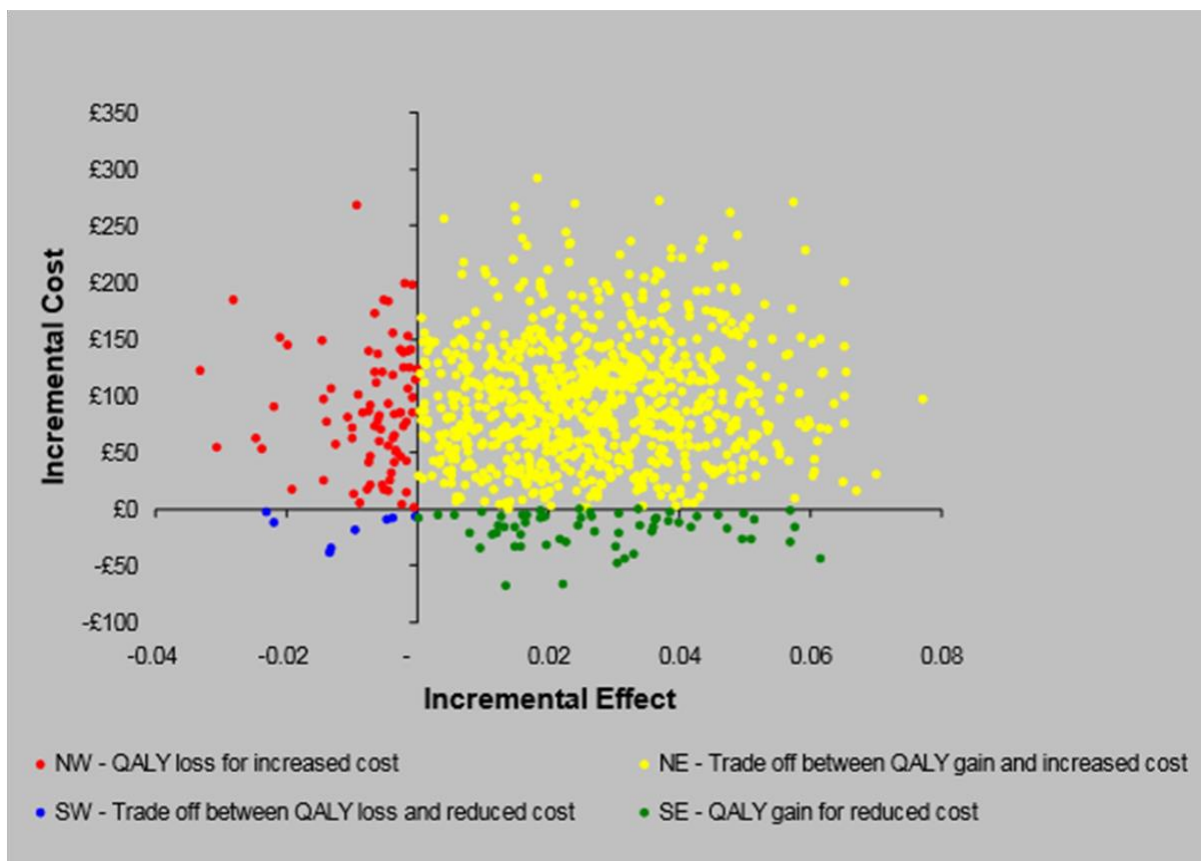


Figure 11 - The cost-utility plane from Edwards et al. ^{cxliii}
 Procedures that fall in the bottom right quadrant are the most cost-effective whereas those in the top left are more expensive and negatively impact on quality of life.

When comparing the cost-effectiveness of two interventions an incremental cost-effectiveness ratio (ICER) is used. This is a ratio of the difference in cost between the two interventions. The ICER is the cost of an intervention's effect in obtaining an improvement in one unit of health. This is also known as cost-utility analysis. ICER depends on their being large cost and effect differences between treatments otherwise the results may be skewed.

Calculating Cost in the UK

In the UK the National Health System (NHS) provides a free health service to patients. This system is taxpayer funded and therefore the NHS faces the challenge of increasing costs, partly due to an ageing population who is living longer after retirement but also due to the increasing price pressures of new treatments

In 2010, 'Payment by Results' (PbR), was introduced by NHS England. This is the payment system in England under which commissioners pay healthcare providers for each patient seen or treated, taking into account the complexity of the patient's healthcare needs. In the NHS, commissioning and provision of healthcare are carried out by two separate organisations. PbR is the way these two entities interact. PbR provides around 60% of the income of a hospital and the price depends on the complexity of treatment.

The system uses pre-determined tariff prices for every procedure, visit and diagnosis. When a patient is discharged, a clinical coder working in the hospital translates their care into codes using two classification systems, ICD-10 for diagnoses and OPCS-4 for interventions. This in turn gets sent to a central database and the hospital gets paid for delivering the treatment.

This variety in costs between different units providing similar services makes it difficult to analyse expenditure and make financial planning. Healthcare Resource Groups (HRGs) are the method used by the NHS to standardise costing. They are used as a standard unit of currency for PbR by healthcare providers. With HRGs, similar conditions and treatments are grouped together to facilitate the process of payment as well as for cost analysis and for comparisons between treatments and different providers. The tariff within each HRG is the national average cost for all hospitals in the UK. The latest version, HRG4, has been in use for payments since 2009 when PbR was introduced by the Department of Health.

Best practice tariffs have also been introduced in 2010, which ensures that tariffs are determined by best clinical practice rather than average cost. A 'market forces' factor is then applied to the tariff which reflects the different costs of delivering care in different centres around the country.

These tariff reimbursement schedules however, have the disadvantage that they often do not reflect the true hospital costs. This is because the real costs that the hospital incurs can be different to the agreed price and also due to the fact that cost calculations are not standardised across the NHS.^{cxliii,cxliiv} HRGs do not capture certain clinical information which can be an important factor in cost calculations such as length of stay per patient or number of investigations acquired during their stay. To address this, Patient Level Information and Costing System (PLICS) has been introduced across the UK since 2009. With this system, actual patient interactions can be mapped and billed accordingly rather than having a fixed set price for all. About 70% of the NHS health care providers use PLICS which is essentially an IT software system used to record and calculate costs.^{cxlv}

There are various factors influencing cost of surgical treatment. There are patient related factors such as preoperative comorbidities and performance status and non-patient factors such as supply costs and hospital overheads. Larger hospitals tend to have higher costs as they take on more complex procedures (dis-economy of scale).^{cxlvi} In addition, one must also consider the indirect medical costs of treatment include factors that are not directly billed to the hospital but are still costly either to the patient or to society in general. These include time off work and income lost due to the operation and the recovery period. Payment for child minding or carers for any dependants whilst the patient is unable to look after them. It also includes health gains if patients' symptoms are controlled with treatment and able to return to work and have reduced ongoing healthcare costs such as medication.^{cxlvii}

Cost also varies from centre to centre. This is not simply due to the different 'market force' factor between centres but also due to the different ways of management by the hospital staff and operating neurosurgeons. For instance, some centres admit patients on the same day of surgery whilst others admit the night before simply due to the distance the patient lives from hospital that might make same day travel impossible.

The cost to perform a laminectomy or inserting an X-Stop device in a patient with LSS includes direct medical costs and indirect costs. Direct costs include length of hospital stay, operating time and theatre time, costs of instruments and devices used, medical staff including surgeons and nurses as well as other healthcare providers including physiotherapists. Any complications arising from surgery can increase these costs by increasing length of stay and the cost of treatment delivered such as drugs. Other direct medical costs include emergency department and outpatient visits, diagnostic tests (including radiographs, MRI, CT and electromyography) and medications which may also involve injections.

In England, all NHS service providers belong to the Clinical Negligence Scheme for Trusts. This scheme is set up to indemnify trusts against successful claims for clinical negligence. It is a nationally administered scheme to which is paid an annual premium and where each trust negotiates its own membership contribution. It is an overhead applicable to all patients and prior to the introduction of PLICs this would not have been identified as a separate cost type but would have been absorbed into other costs. Although the cost is spread equally amongst patients

irrespective of what procedure they've had done (except maternity and emergency services) it still varies amongst different trusts depending on what deal they've negotiated with their insurance provider. This means that indirect costs vary amongst different hospitals.

Cost-effectiveness in the Management of LSS

The outcome of surgery or any intervention for LSS can be measured as QALY gained. It is important to have this data available as QALYs can be used as a resource allocation guide and policy makers may use it to make decisions on funding. Calculating QALYs in LSS can be challenging since LSS mainly affects patients who are no longer in the workforce and who are often affected by other co-morbidities that may affect their quality of life.

Burnett et al looked at cost effectiveness between laminectomy and X-Stop.^{cxlviii} This publication was a retrospective review of published studies however a hypothetical cost effectiveness model was created by the authors based on a patient being treated in the US using the Medicare national average reimbursements. The healthcare cost calculation system in the US has many differences to that in the UK. One of the differences is that length of hospital inpatient stay does not alter the payments received and this was therefore not reflected in this cost effectiveness model.

The cost of a laminectomy in the US, as mentioned previously, was estimated to be between \$12,615 and \$27,055.53.^{cxlix} It is generally agreed by policymakers that for a treatment to be considered as cost effective, the cost of QALY gained as being \$100,000 for a treatment to be considered cost-effective in the US. The main source of this is from the SPORT trial.

No data exists with regards to the cost and cost effectiveness of lumbar spinal stenosis surgery in the UK to date. The CELAX trial aims to address specifically this missing piece of information.

The Cost-effectiveness and Quality of Life after Treatment of Lumbar Spinal Stenosis with the Interspinous Distractor Device (X-Stop) or Laminectomy (CELAX) : A Randomised Control Trial

The idea to design, set up and conduct this trial came about in 2008 when many patients in the UK were undergoing IDD insertion with mixed results. The cost of the device was much higher than a laminectomy but the time taken to insert it was much less. We conducted a literature review and identified that there was no UK data on cost effectiveness between the two procedures.^{cl} A Cochrane review published in 2005 concluded that there aren't enough RCTs addressing which form of surgery is more cost effective for LSS and that surgeons ought to be encouraged to conduct trials in this field.^{cli} NICE guidelines published in 2005

(www.nice.org/guidance/ipg365/history) advised that long term follow up was lacking and the use of IDD's should only occur within a research trial.

Due to the gap identified in the literature on cost effectiveness of LSS surgery in the UK, and due to the rising popularity of IDD's, the CELAX trial was designed to answer whether the most widely used device, the X-Stop, was as cost effective as the gold standard laminectomy. This was a randomized control trial where patients with LSS who were eligible to have both procedures, laminectomy or X-stop insertion were randomly allocated to one operation or the other.

Methods

This was a randomised controlled multicentre trial carried out in three NHS trusts. The first patient was included on 15th December 2008 whilst the last patient was included on 13th February 2014. Interim analyses were performed in June 2012.

Objectives

The main objective of the study was to answer the null hypothesis that: “There is no difference in cost effectiveness of the X-Stop device compared to that of conventional decompressive surgery.”

The null hypothesis is rejected if the mean cost of treatment in the X-Stop group is significantly different to the Laminectomy surgery group. Two-way analysis of variance is performed to determine any statistically significant difference between the mean costs of treatment in the X-Stop and decompression groups ($p=0.05$).

The following end points were set out:

Primary endpoint - To determine if there was a difference in cost-effectiveness between the two operations.

Secondary endpoint - To determine if there was a difference in outcomes of quality of life between the two operations.

Other endpoints - To determine if there was a difference in the complication rates between the two operations.

Study Design

CELAX was a randomised control trial conducted in three centres in the UK. It consisted of two surgical arms: Laminectomy and X-Stop with two years of follow up. Ethics approval was obtained for each of the three participating centres.

Centre 1 – The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS foundation trust, London, UK.

Centre 2 – St’ George’s University Hospital NHS foundation trust, Tooting, London, UK.

Centre 3 – Hurstwood Park Neurosciences Centre, Brighton and Sussex University Hospitals NHS trust, Haywards Heath, UK.

This study was designed by Mr. David Choi, the chief investigator with initial sponsorship by Medtronic Inc. between 2008 and 2010. Mr. Besnik Nurboja was the researcher for the trial between 2008 and 2010 and recruited

ten patients. I was the researcher from 2010 until study completion and recruited all the remainder patients. In 2012 Mr. Nurboja conducted an interim analysis. The sample size calculation was re-adjusted by Mr. David Choi (supervisor) and UCL statistics support.

Patients were referred through the normal NHS pathways and underwent assessment and diagnosis of LSS. No additional investigations were required as a result of study participation. Referrals from general practitioners and other specialists were screened by myself every week at the three participating centres. Referral letters that described features of LSS were booked into the CELAX outpatient clinics (clinic codes: DC406 at centre 1, FJ03 in centre 2 and CELAX in centre 3). I attended three weekly clinics (one at each centre) where on average five patient slots were available for booking for each clinic. An estimated 300 patients were screened by myself over the study period. Patients were also followed up in these three weekly clinics.

Sample size calculations were modelled on the study by Katz et al.^{clii} This is based on a type I error estimate of 0.05 and type II estimate of 0.2. This means that a sample big enough to detect a difference in cost of at least 20% between the two operations was needed, with a significance level of 5%. Based on this calculation, initially a sample size of 110 patients (55 in each arm) was estimated but this was adjusted to 50 patients (25 in each arm) after the interim analysis of Mr. Besnik Nurboja, when it became clear that the rate of recruitment was slower than predicted.

A randomised design was used with a block size of ten, and a 1:1 treatment allocation which were obtained using a computer random number generator. Allocations were stored in coded and sealed envelopes. Each envelope was opened the day before surgery and the patient was informed on their admission.

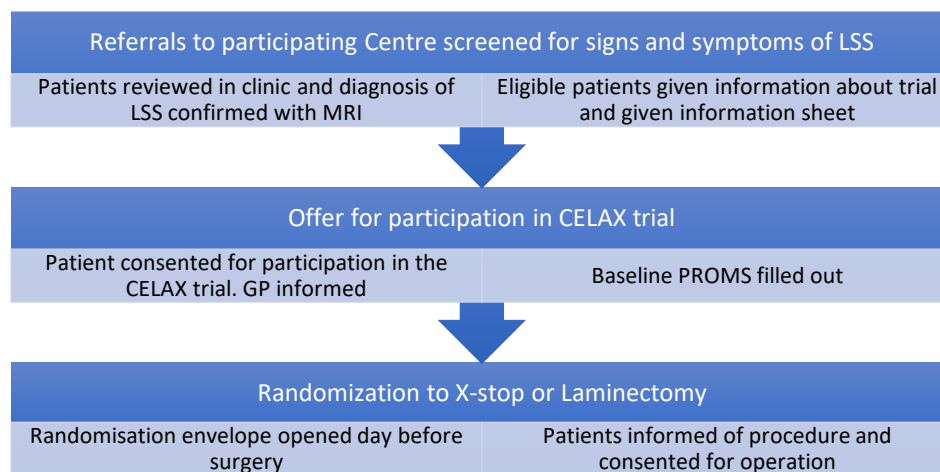


Figure 12 - Trial Flow chart

Ethics and Regulatory issues

Approval for the study was granted by The Charing Cross Research Ethics Committee in 2008. (Reference number: 08/H0711/12.) Patients provided written consent before entering the trial.

Participants in the CELAX trial needn't go through any additional investigations or follow up than if they weren't part of the trial. However, compared to non-participants they were required to accept the fact that their operation was selected at random and that they were unable to choose which operation to undergo themselves. In two of the centres, Centre 1 and 2, the X-Stop device was also offered to patients outside the trial and therefore those who did not want to participate in the trial could choose to either have the device insertion or to undergo a laminectomy. In Centre 3 the X-Stop device was only allowed to be used within the CELAX trial. This meant that patients who refused to participate in the trial could only choose to undergo a laminectomy. In addition, participants also agreed to complete a set of questionnaires pre-operatively and at six months, one year, and two years' post-operative time points.

The trial was registered with the National Institute for Health Research (NIHR) - ISRCTN88702314. The investigators on the trial all completed Good Clinical Practice (GCP) training.

All trial participants signed a consent form declaring their agreement to be part of the trial and for their data to be used for analysis. In addition, all patients undergoing an operation also signed the respective trust's surgical consent form. Withdrawal from the trial was an option at any point.

During the consent process, it was explained to patients that there is no hard evidence in the literature that one surgical option was superior to the other however, the gold standard operation is a laminectomy. It was also explained that some surgeons have fallen out of preference for the device and have stopped using it. The safety profile of the X-Stop was confirmed by the FDA and by NICE and the clinical efficacy was reported to be similar to that of a laminectomy at approximately 70% success rate for symptom improvement.

Patient population

Patients referred to the neurosurgical outpatient department in the three participating centres were screened for symptoms of LSS. Patients who reported symptoms of neurogenic claudication underwent an MRI scan. Almost invariably patients had already undergone this imaging modality by the referring physician. Those patients diagnosed with LSS were screened for eligibility in the CELAX trial. Eligible candidates were offered to participate in the trial and were given a patient information sheet. As per the Good Clinical Practice guidelines (GCP), patients were allowed enough time to think and consider the information provided and allowed to withdraw their consent in participating in the trial. There was no observational cohort in this trial and therefore patients who did not agree

with the randomisation process were not included in the study and no data was collected. Study participants were asked to fill out preoperative questionnaires which were then repeated after six months from surgery, one year and two years.

Inclusion criteria

Patients whose symptoms and imaging supported the diagnosis of LSS were invited to participate in the study if the following conditions were met:

- a) Male or non-pregnant female patients
- b) Above the age of 18
- c) BMI <35 kg/m²
- d) Leg pain with or without back pain of greater than 6 months' duration, partially or completely relieved by adopting flexed posture and who are suitable candidates for posterior lumbar surgery
- e) Completed at least 6 months of conservative treatment without obtaining adequate symptomatic relief
- f) Degenerative changes at 1 or 2 adjacent levels between L1-S1 confirmed by MRI scan with one or more of the following:
 - decrease in disc height > 50%
 - annular thickening
 - degenerative spondylolisthesis up to Meyerling grade 1 or less
 - thickening of ligamentum flavum
- g) Physically and mentally willing and able to comply with the postoperative scheduled clinical and radiographic evaluations.

Exclusion criteria

The following conditions precluded participation in the trial:

- a) Fixed motor deficit
- b) Skeletal immaturity
- c) Previous lumbar spinal surgery

- d) Obvious signs of psychological or worker compensation or litigation claims elements to their condition
- e) Unwilling or unable to give consent or adhere to the follow-up programme
- f) Active infection or metastatic disease
- g) Non-degenerative spondylolisthesis
- h) Degenerative spondylolisthesis > Meyerding Grade 1
- i) Known allergy to implant materials
- j) Severe osteoporosis, rheumatoid arthritis or achondroplasia
- k) Cauda equina syndrome
- l) Acute disc extrusion or sequestered fragments

The above eligibility criteria were designed to remove confounding factors such as significant spondylolisthesis, scoliosis and osteoporosis that could increase the risk of complications and have an impact on patients' outcome thus skewing the data and masking the effects of surgery. Participating candidates were required to be eligible for both operations with no obvious benefit in undergoing one operation or the other. If a patient clearly benefitted from having a standard laminectomy rather than the X-stop, such as in cases of osteoporosis then participation was not offered. Equally if there were cases for instance of high anaesthetic risk that would benefit from the shorter and less invasive X-stop procedure, these patients were also not offered to participate in the trial.

Preoperative assessment

Patients who met the eligibility criteria and agreed to participate in the trial underwent a preoperative assessment for fitness for a general anaesthetic. Anti-platelet drugs and anti-coagulants were stopped 7 days prior to surgery in Centre 1 and 3 but this was not trust policy in Centre 2. Patients with multiple co-morbidities who were deemed to be at increased risk (ASA grade 3 or more) were referred for an anaesthetic review for optimisation prior to surgery.

Follow up

Routine follow up 6 weeks and then 6 months after surgery was organised for all participants. This was in line with standard NHS follow up. After 12 months and 24 months, patients were contacted by phone or sent a postal set of questionnaires.

Compliance and Withdrawal of participants

Each participant was asked to complete each questionnaire pre-operatively, anytime between recruitment and surgery, and again after six months, one year and two years. Participation was voluntary and every participant had the option to withdraw at any time.

Adverse Events

1. The WHO defines an adverse event as any undesirable occurrence in a patient or study subject associated with the use of any medical product but not necessarily causally related. This is considered as a serious adverse event when it results in death, disability, prolonged hospital stay, congenital defects or if it necessitates intervention to prevent permanent effects. (who-umc.org).

Study Measures

The primary outcome measure was cost-effectiveness therefore the main outcome measures were quality of life and cost. Quality of life was measured using quality-adjusted life-years (QALYs), based on EuroQol (EQ-5D) utility index (United Kingdom, time trade-off tariff) measured at baseline, 6 months, 12 months and 2 years. Cost was measured per patient episode as detailed below.

In the CELAX study the following PROMS were used:

General Health -

- 1)EQ-5D* and
- 2) The 36-item short form health survey (SF36)

*The UK weighted scoring algorithm was used to interpret data.

Disease specific -

- 1) Zurich Claudication Questionnaire (ZCQ),
- 2) Oswestry Disability Index (ODI) and
- 3) Quebec Back Pain Disability Scale (QBPDS).

The choice of these PROMS was based on the instruments used by the NICE guidelines to measure outcomes in LSS (ODI and ZCQ) and on several health economic studies where QALYs are calculated (EQ5D and SF36).^{cliii}

Cost Calculations

Cost details were provided by the cost accountants from the finance department of each centre. The detailed costs per patient were available for Centre 1 as this hospital uses the PLICS database for reimbursement. Centre 2 and Centre 3 only use HRGs to receive their income and therefore they could not provide patient level details of cost. These hospitals get paid the same amount for all patients coded under the same HRG, which is based on the national tariff for that operation corrected with the marketing force factor for that centre.

This means that what the hospital spends for a patient's spell is different to what the hospital gets reimbursed. For instance, the cost of the X-Stop device is not included in the coding for the insertion of an interspinous device. In addition, the OPCS for a laminectomy operation (V254) and an X-Stop insertion (V281) are grouped under the same HRG code (HC63) which means the cost accountants cannot tell the difference between the two operations financially. Since charges and fees differ from real cost, the price for operating theatre time per minute and the price per day of admission was used to estimate the cost per patient. This was also done so as to standardise cost estimation between the different centres.

Each patient also had an additional cost of being included in the clinical negligence scheme which also varies according to the trust. The data was given as a cost unit which was then given a monetary value which varied according to the financial year. All costs were expressed in 2008 GBP (£)

The following were the prices given for 2010 with the adjusted marketing force factor. An adjustment of 2% inflation per year was used:

Centre 1

Operating time £17.98/min, Admission £188.16/day

Centre 2

Operating time £16.79/min, Admission £175.61/day

Centre 3

Operating time £14.99/min, Admission £156.80/day

Cost per minute for theatre time includes theatre staff, medical staff and overheads related to theatres. Ward Costs were given as cost per bed day. This includes ward nursing staff and overhead costs related to wards. It does not include however, medical staff costs.

The cost of the X-Stop device was £2605 which was added on to the total cost of the X-Stop patients. This was doubled in patients who had two levels operated on.

Secondary Measures:

In addition, the following measures were recorded prospectively; theatre time, length of stay, post-operative complications and adverse events.

Theatre time was considered from arrival to the anaesthetic room to departure. This was because the cost of theatre time does not distinguish between operating time and anaesthetic time. Length of stay was measured in whole days spent in hospital post-operatively including day of operation and day of discharge therefore 24 hours counts as one day. Complications and adverse events were recorded from the case notes and from follow up visits.

Post-operative imaging is not routinely obtained in the NHS following non-instrumented spine surgery. Therefore, CELAX patients did not undergo post-operative MRI scans unless there were reported problems such as ongoing or worsening symptoms. For this reason, radiological changes in canal diameter and neuro-foraminal height were not measured. The outcomes of the CELAX trial were all clinical, subjective, patient responses.

Statistical Analysis

Analysis was performed with both the intention to treat principle and as-treated principle. Pre-operative data was checked for normality. The main analysis was to look for a significant difference between the quality of life at baseline and at 24 months after surgery between the two operations.

The two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to check for any significant variation between the baseline scores of the two groups. Since the data was not normally distributed, the non-parametric paired Wilcoxon signed-rank test was used to check for significance between the baseline and the post-operative scores.

A general linear regression model was used to assess the effect of other predictor variables on outcome.

QALYs were calculated using the area under the curve method by plotting the quality of life utility index over the study time points. QALY's gained and cost per QALY were calculated for each participant over the study period based on their last EQ5D response.

The cost-effectiveness ratio was calculated by comparing the mean cost per QALY of both operations.

All analyses were performed using STATA 14 and Microsoft Excel for Mac.

Results

Out of approximately 1000 referral letters screened, an estimated 300 patients were reviewed by myself in one of the three trial clinics (on average 3 new patients a week for two years). A total of fifty-six patients were found to meet the criteria for inclusion in the CELAX trial and were offered to participate. Forty-nine patients were randomised and 7 opted for conservative treatment. Twenty-seven were randomised to a Lumbar laminectomy and twenty-two were randomised to the X-stop arm. Of these, twenty-six had a laminectomy and twenty-one had an X-stop insertion. (*Fig. 13*) Three patients died during the study period due to unrelated causes. One X-stop patient decided to withdraw after 6 months and one laminectomy patient was lost to contact.

Patient characteristics

The age range was 47-86. Eighteen were female and 29 males. (Table 3) Radicular symptoms were present in 78.7% and 74.5% also complained of back pain. LSS was confirmed with MRI findings. Spondylolisthesis was present in 6 patients (5 - X-Stop, 1 – Laminectomy). No statistically significant intergroup differences were noted in the presence of co-morbidities, severity of symptoms and number of treated levels, however musculoskeletal co-morbidities were more frequent in the X-Stop group (10 vs 2). Grade I spondylolisthesis was also more prevalent in the X-Stop group (5 vs 1). The mean pre-operative scores of the ZCQ questionnaire were slightly worse in the X-Stop arm (73.3% X-Stop vs 70.1% laminectomy for symptom severity (diff 2.84, SE 3.79) and 66.78% vs 60.48% for physical functioning (diff 8.6, SE 4.8).

Surgical treatment and complications

The mean surgical time for the laminectomy group was 121.78 minutes (SD 37.27min, 95%CI 105-137min) and for the X-stop group 65.85 minutes (SD 20.84min, 95%CI 56-75min). An unpaired Student T-test showed that the operation time was significantly longer for the laminectomy group (T score = 6). Sixteen out of the 21 X-Stop operations were carried out by a consultant whereas only 8 laminectomies were carried out by a consultant. None of the patients required a blood transfusion. There were no perioperative deaths. Peri-operative and post-operative complications are listed in Table 5. There were 5 complications in the laminectomy group and in two of the X-Stop patients, giving a total complication rate of 14.89%. Reoperation occurred in 5 patients within the study period; 4 of the reoperations were for removal of the X-stop and decompression at the same level. The other reoperation was for CSF leak repair post laminectomy. In total, there were five cross overs from the X-Stop arm to the laminectomy arm, four were due to re-operations and one was due to breakage of the spinous process during insertion of the spacer.

The average length of stay in hospital was 4.176 days for the X-Stop group (1-20 days) and 4.26 days for laminectomy (1-15 days). The distribution of the length of stay was similar in the two groups with the majority of patients being discharged the following day (36% laminectomy group vs 43% X-Stop group). (*Fig. 21 b*) There was one complication per group that resulted in a prolonged length of stay and therefore increased the mean to 4 days

in both groups. Fischer's exact test showed no significant difference between the length of stay in the two groups (Pr=0.404).

Adverse Events

Laminectomy group n =

x1 Myocardial infarction a few hours post op, requiring emergency stenting

x1 CSF leak post op requiring antibiotics and re-operation for repair

X-Stop group n=

x1 Spinous process fracture during insertion, procedure converted to laminectomy

x1 Prolonged hospital stay due to severe back pain

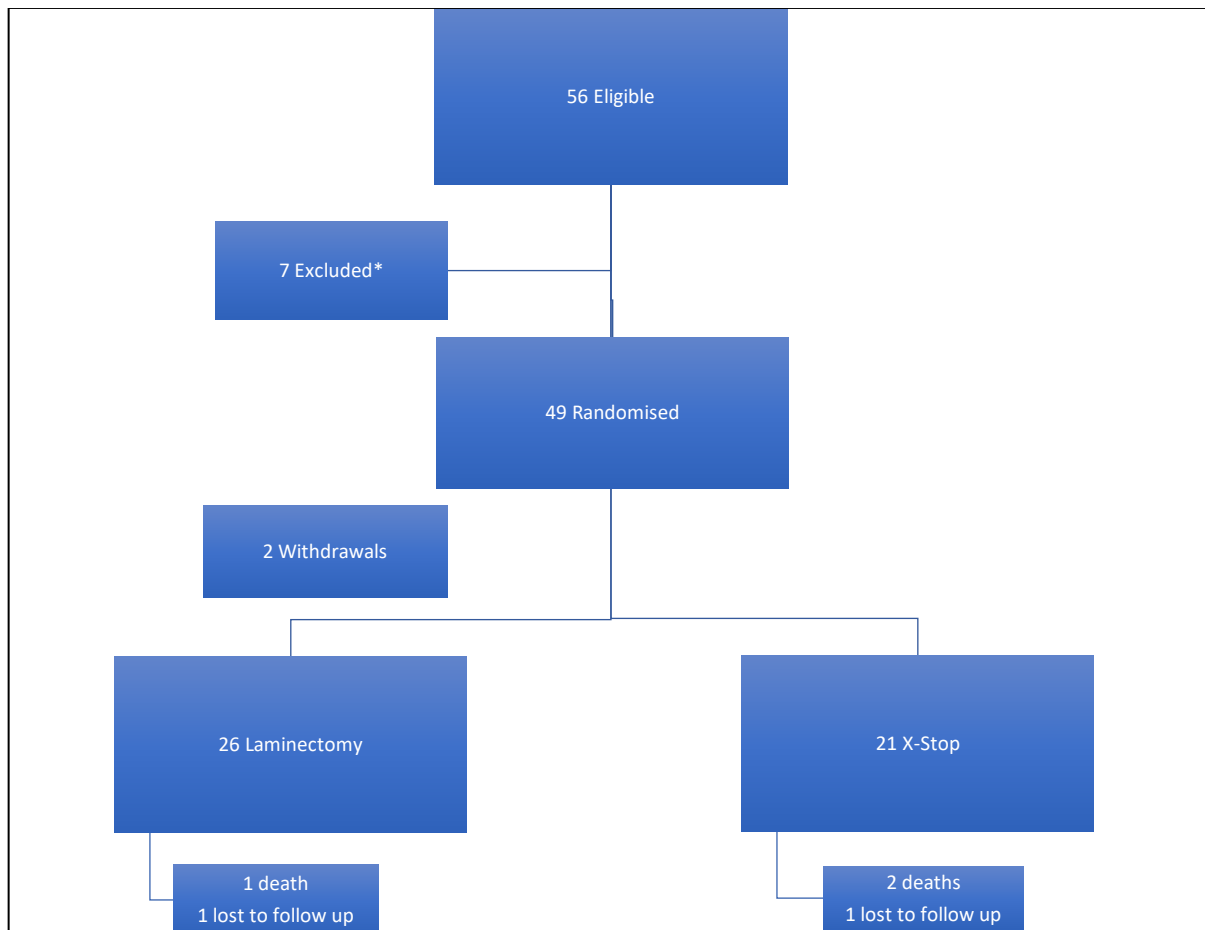


Figure 13 – Flow diagram depicting the enrolment process. (* 7 patients opted for conservative treatment. Two patients withdrew after randomisation but prior to surgery. Three patients died (2 X-stop, 1 laminectomy), one X-stop withdrew after 6 months and one laminectomy was lost to follow up.)

Non-adherence to treatment

Seven patients were recruited into the trial but did not reach the randomisation stage as they changed their mind about surgery and decided to opt for non-surgical treatment. One patient withdrew from the study after being randomised to the Laminectomy arm and sought the X-stop device insertion privately. Another patient who was randomised to the X-Stop arm did not go ahead with the trial as the X-Stop was not available on the day of surgery. (Fig. 13)

Of the 21 patients who were underwent X-stop insertion, one patient refused to complete the follow up questionnaires beyond the six months. One patient from the 26 who underwent a laminectomy was lost to follow up after surgery. This patient also had an MI in the early post-operative period and was transferred to the cardiac services. Contact was lost from then onwards.

Two patients from the X-Stop arm and one from the laminectomy arm died during the study period due to unrelated causes. At each time point after recruitment there was no obvious difference between the rates of missing data and drop outs between the two arms.

Operated patients:

Centre	Laminectomy	X-Stop
<i>NHNN</i>	9	9
<i>ST'G</i>	11	8
<i>HWP</i>	6	4
Total	26	21

A)

LAMINECTOMY GROUP N = 26X-STOP GROUP N = 21

<i>DEMOGRAPHIC CHARACTERISTICS</i>		
AGE RANGE	51-84	47-86
MEAN AGE	69	70
MALE / FEMALE	17 / 9	12 / 9
CO-MORBIDITIES	9 nil, 9 minor, 8 serious/multiple	7 nil, 5 minor, 10 serious/multiple
<i>HYPERTENSION</i>	8(31%)	5(24%)
<i>RESPIRATORY</i>	2(8%)	2(10%)
<i>DIABETES</i>	3(12%)	2(10%)
<i>OBESITY(BMI >30)</i>	1(4%)	2(10%)
<i>CARDIOVASCULAR</i>	8(31%)	7(33.3%)
<i>SMOKER</i>	2(8%)	1(5%)
<i>MUSCULOSKELETAL</i>	2(8%)	10(48%)
EMPLOYMENT	No 23, Yes 3	No 19, Yes 3

BASELINE CHARACTERISTICS

NUMBER OF OPERATED LEVELS	16 Single, 8 two levels, 2 three levels	15 single, 6 two levels
L2/3	2	1
L3/4	13	11
L4/5	20	14
L5/S1	0	1
SPONDYLOLISTHESIS GRADE 1	1	5

B)

PRE-OP SCORES

MEAN	LAMINECTOMY	X-STOP	
QUALITY OF LIFE			
EQ-5D			Diff (SE)
<i>TTO SCORE (UK)</i>	0.298	0.202	-0.096 (0.102)
<i>BEST IMAGINABLE HEALTH STATUS</i>	66.6	52.63	
SF36			
<i>PHYSICAL FUNCTIONING</i>	26.6	21.31	
<i>ROLE PHYSICAL</i>	22	13.15	
<i>BODILY PAIN</i>	30	24.89	
<i>GENERAL HEALTH</i>	57	55.89	
<i>VITALITY</i>	45.4	39.21	
<i>SOCIAL FUNCTIONING</i>	56.5	37.5	
<i>ROLE EMOTIONAL</i>	51.99	35.07	
<i>MENTAL HEALTH</i>	67.52	57.47	
DISEASE SPECIFIC			
ZCQ			
<i>SYMPTOM SEVERITY</i>	70.46%	73.31%	2.84 (3.79)
<i>PHYSICAL FUNCTION</i>	58.17%	66.78%	8.6 (4.8)
ODI	43.25%	48.99%	5.74 (4.88)
QBPDS	58.18%	64.32%	

Table 3 –A) Summary of Demographics and Patient Characteristics at Baseline. B) Mean pre-operative scores. None of the questionnaires had preoperative scores which were significantly different between the two groups.

<i>Operative results</i>		
	<i>Laminectomy</i>	<i>X-Stop</i>
Operating Time-mean (min)	121.78 (SD 37.27 95%CI 105-137min)	65.85 (SD 20.84min 95%CI 56-75)
<i>Length of Stay- mean (days)</i>	4.26 (SD 3.64)	3.8 (SD 4.12)
<i>Total Cost –theatre time (£)</i>	1970.03 (SD 581.88)	1112.08 (SD 498.15)
<i>Total Cost – Admission (£)</i>	741.77 (SD 707.72)	686.92 (SD 791.03)
<i>Complications (No.)</i>	5(19.2%)	2(9.5%)
<i>Seniority of Surgeon</i>	8 consultant 18 Spr	16 consultant 5 Spr

Table 4 – Operative results for the two surgical arms; Laminectomy and X-Stop

Surgical Arm	Complications	Total (%)
Laminectomy	X 3 dural tears X 1 CSF leak requiring further admission and reoperation X 1 MI post op	5 (19.2%)
X-Stop	X 1 worsening back pain immediately post op X 1 break in spinous process	2 (9.52%)
Total		7 (14.89%)

Table 5 – Operative complications for both surgical arms. (%) Rate per surgical arm. (Pearson’s coefficient 0.654)

Results Laminectomy Vs X-Stop Intention to treat analysis – Mean scores

	Preop		6 months		1year		2 years	
	Laminectomy	Xstop	Laminectomy	Xstop	Laminectomy	Xstop	Laminectomy	Xstop
SF36	30	24.9	42.2	42.6	43.7	51	43.5	49.5
Bodily pain								
Physical function	26.6	21.3	41.8	42.3	41.8	47.9	39.1	42.9
EQ5D	0.29	0.20	0.47	0.45	0.53	0.41	0.58	0.45
P value			0.04	0.006	0.002	0.39	0.0008	0.07
ZCQ	70.1	73.3	57.3	57.1	57.3	51.5	59.3	57.8
Symptom severity								
Physical function	60.5	66.8	48.2	54.9	50.3	46.4	56.9	48.5
Satisfaction	N/A	N/A	54.5	56.9	58.6	47.3	59.6	52.7
QBPD	58.2	64.3	44.5	49.8	55.3	44.5	59.2	41.4
ODI	44.9	48.9	37.1	37.1	42.1	30.5	44.4	37.5

Table 6 - Mean scores for General Health and Disease Specific Questionnaires – P values indicate difference from baseline.

Primary Outcomes

EQ5D Scores

Below is a box and whisker plot (Fig. 14) showing the distribution of the EQ5D TTO scores between the two groups. The pre-operative scores are slightly worse in the X-Stop group however the mean scores become more similar over time.

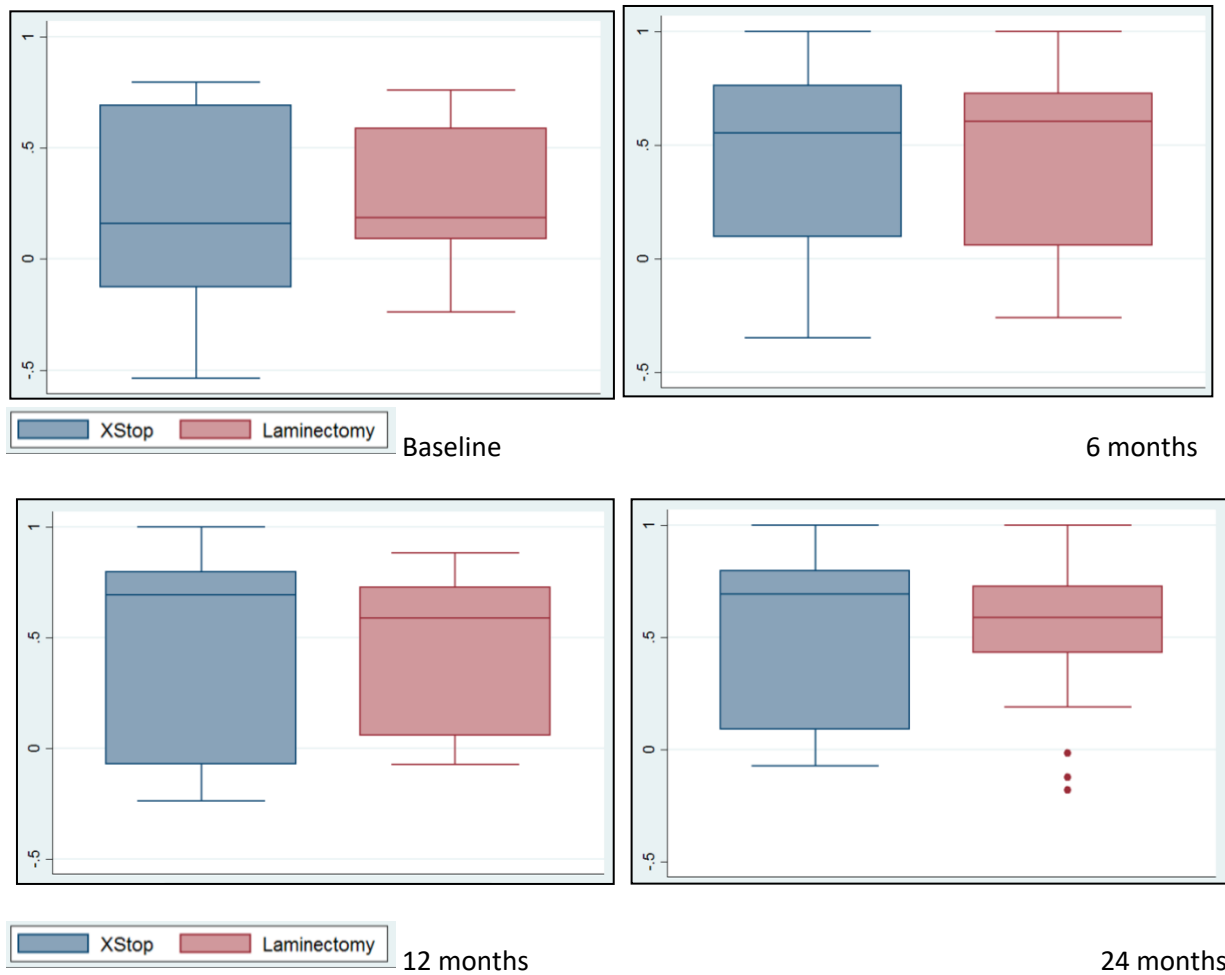


Figure 14 – Comparison of EQ5D scores between the Laminectomy and X-Stop groups at baseline, 6 months, 12 months and at 24 months. The Y-axis represents the EQ5D score which ranges between -0.594 (worst health) to 1 (full health).

Figure 15 below is a schematic representation which shows the distribution of replies to the EQ5D questionnaires at different time points. The pre-operative scores show a similar distribution in replies between the two surgical arms which is what is expected with randomisation. However, the X-Stop group have slightly worse scores for 'self-care'. At every post-operative time point there are no scores of 3 (green bars) for mobility in both groups. In general, there is an increase in the size of the blue bars post-operatively most significant in the 6-month postoperative period but maintained throughout the study period. There was no statistically significant difference between the pre-op TTO scores of the two groups.

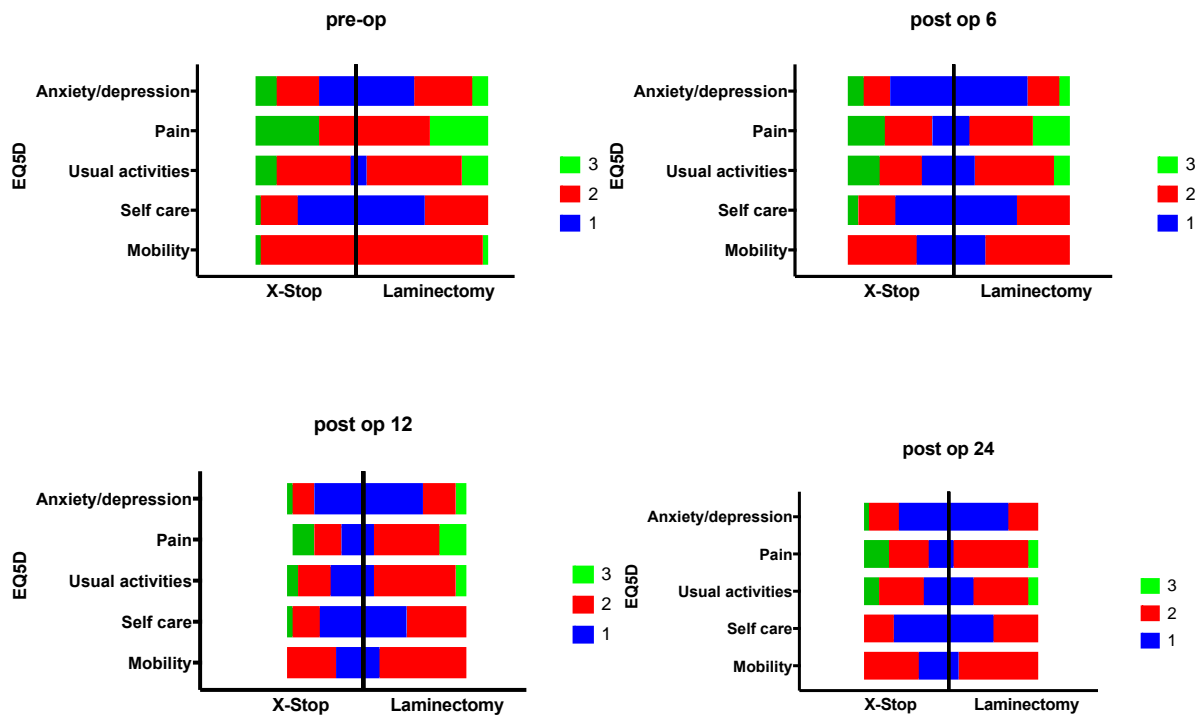
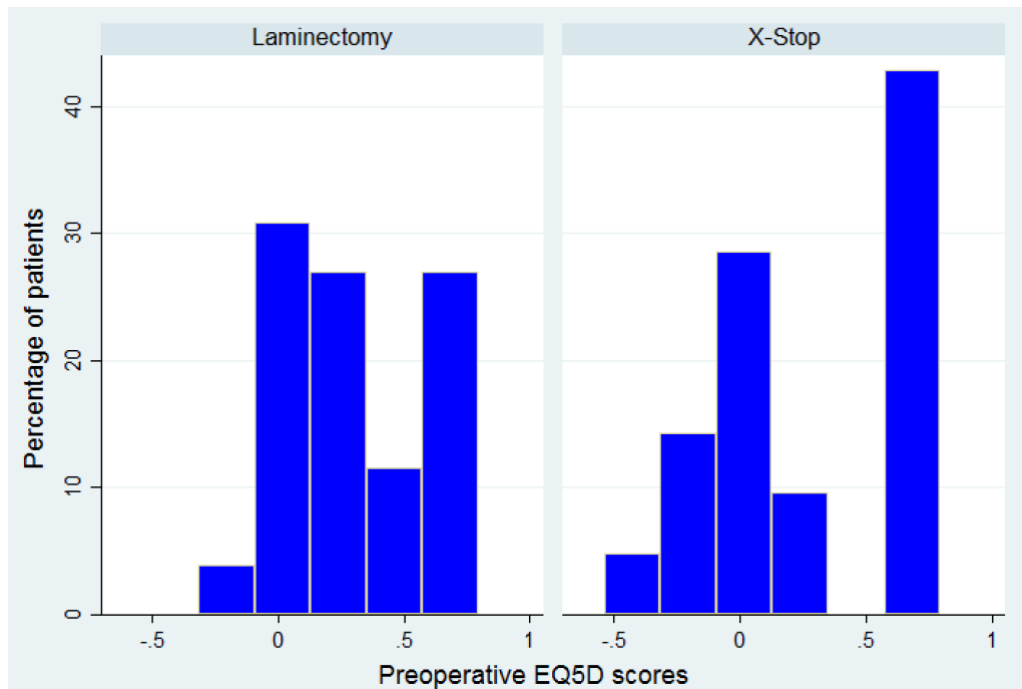


Figure 15 - Detailed scores of EQ5D: 1 – I do not have any problems, 2 – I have some problems, 3 – I have severe problems.



A

Two-sample Wilcoxon rank-sum (Mann-Whitney) test			
Operation	obs	Rank sum	expected
Laminectomy	26	641	624
X-Stop	21	487	504
combined	47	1128	
Null hypothesis: EQ5D pre op Laminectomy = EQ5D pre op X-Stop			
Probability	0.7151		

B

Figure 16 – A) Histogram showing the distribution of scores. The data is not normally distributed and therefore the Mann-Whitney Test was used to compare pre-operative data B).

There was no statistically significant difference in the preoperative scores between the two groups.

Intention to Treat analysis of EQ5D -

<u>Wilcoxon signed-rank test</u>			
<i>sign</i>	<i>Obs</i>	<i>Sum ranks</i>	<i>expected</i>
positive	6	44	85.5
negative	12	127	85.5
zero	0	0	0
all	18	171	171
Null hypothesis: EQ5D Pre op X-Stop = EQ5D Post Op X-Stop			
Probability = 0.0707			

Paired Wilcoxon signed-rank test for pre-operative and 2 year EQ5D TTO scores for the X-Stop group - P value 0.07

<u>Wilcoxon signed-rank test</u>			
<i>sign</i>	<i>Obs</i>	<i>Sum ranks</i>	<i>expected</i>
positive	4	32.5	149.5
negative	19	266.5	149.5
zero	1	1	1
all	24	300	300
Null hypothesis: EQ5D Pre op Laminectomy = EQ5D Post Op Laminectomy			
Probability = 0.0008			

Paired Wilcoxon signed-rank test for pre-operative and 2 year EQ5D TTO scores for the Laminectomy group – P value 0.0008

As-treated Analysis at 24 months:

<u>Wilcoxon signed-rank test</u>			
<i>sign</i>	<i>Obs</i>	<i>Sum ranks</i>	<i>expected</i>
positive	3	15	45.5
negative	10	76	45.5
zero	0	0	0
all	13	91	91
Null hypothesis: EQ5D Pre op X-Stop = EQ5D Post Op X-Stop			
Probability = 0.033			

Paired Wilcoxon signed-rank test. Pre-operative vs 2 year score. As-treated Analysis for the X-Stop group - P value of 0.033

<u>Wilcoxon signed-rank test</u>			
<i>sign</i>	<i>Obs</i>	<i>Sum ranks</i>	<i>expected</i>
positive	7	73.5	217
negative	21	360.5	217
zero	1	1	1
all	29	435	435
Null hypothesis: EQ5D Pre op Laminectomy = EQ5D Post Op Laminectomy			
Probability = 0.0019			

Paired Wilcoxon signed-rank test. As-treated Analysis. Twenty-nine patients had received a laminectomy at the end of the study period. P value 0.002

The results above demonstrate that when using the EQ5D quality of life questionnaire, both groups showed an improvement overall. However, at 24 months this was only significant for the laminectomy group. For the X-Stop group, the improvement from the mean pre-operative scores to the mean scores after six months shows a statistically significant improvement of 0.19 (P value 0.006). The mean score at 24 months however was 0.17 which was not significant (P value 0.07). For the laminectomy group, the improvement was significant at all post-operative time frames (6 months -0.184 (SD 0.40 $p=0.04$) 12 months 0.26 (SD 0.32 $p=0.002$)). (Table 6)

As-treated analysis was also carried out at two years to account for the five cross overs. This in turn showed statistically significant improvement for both the laminectomy group and the X-Stop group. Therefore, by removing those five patients from the X-Stop group and adding them to the laminectomy group, the improvement becomes more significant for both groups.

At two years, there were 7 X-Stop patients who deteriorated (33.3%) and 14 (66.6%) who improved vs 5 laminectomy patients who deteriorated (19.2%) and 20 (76.9%) who improved overall.

QALY's

QALY's were calculated using the area under the curve method (AUC) for each patient. Example is shown below where the EQ5D TTO score was plotted for each time point:

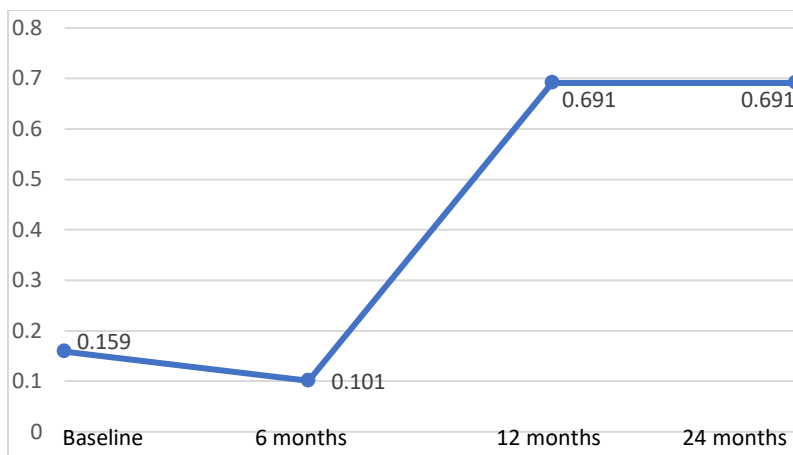


Figure 17 - TTO scores for one participant at different time points: Preoperatively, 6 months post op, 12 months post op and 24 months post op. QALY was calculated by measuring area under the curve.

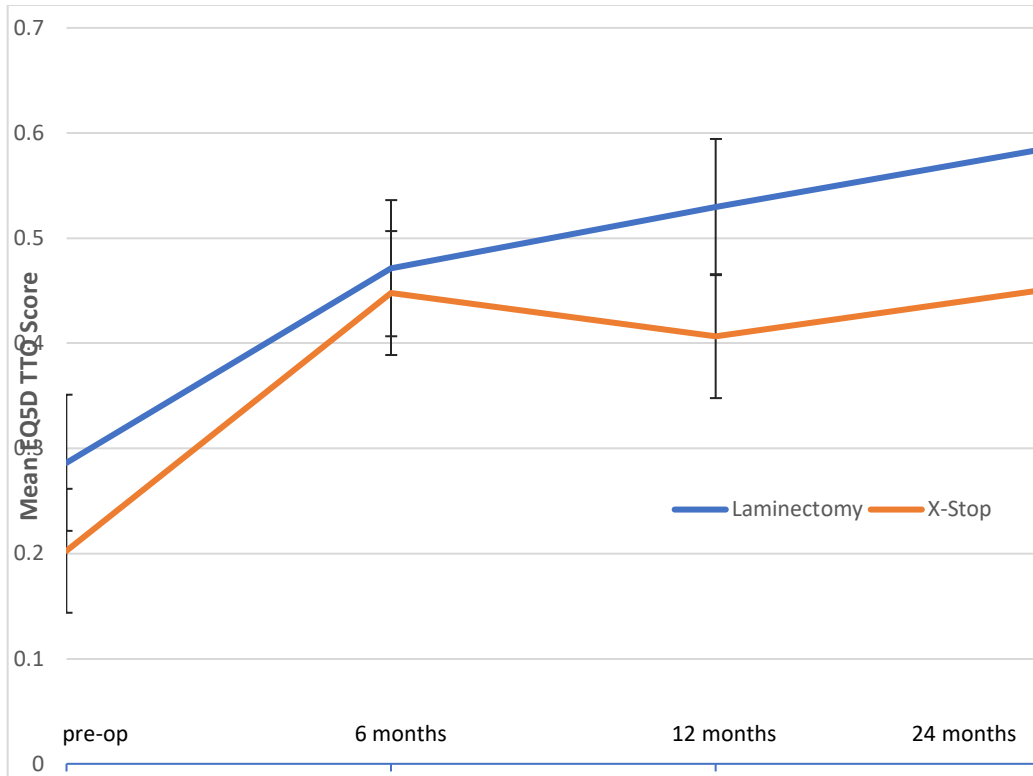


Figure 18 – Mean EQ5D TTO scores and standard error bars over the different study time points.

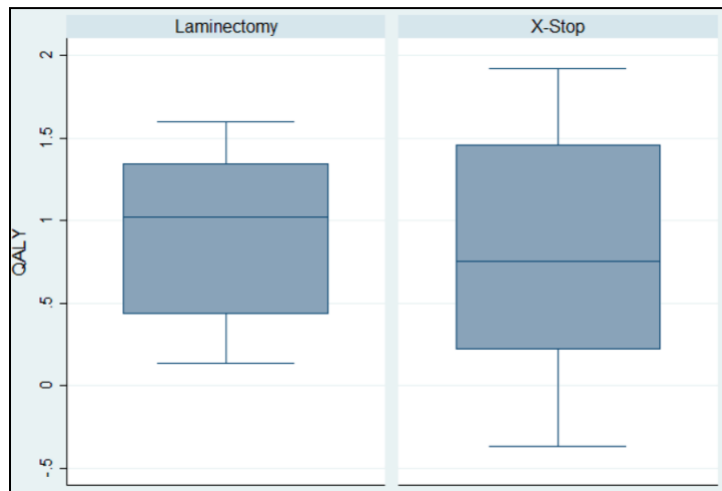


Figure 19 - Box plot of QALYs for both treatment groups with 95% CI for the mean using the EQ5D TTO scores

The mean QALY for the X-Stop group was 0.81 and for the Laminectomy group was 0.92. There was no significant difference between the QALYs of the two groups.

Cost Results

Cost (£)	Laminectomy	X-Stop
Cost Theatre time		
mean	1,970.03	1,112.08
range	1,199.2 – 3,358	539.4 – 1,833.96
Cost of Admission		
Mean	741.77	686.92
range	156.8 – 2,822.4	156.8 – 3,763.2
Cost of Device	-	2,605*
Total Cost	2,711	5,148
	1,356 – 4,800	915 – 4,842**

Table 7 – Cost Results –

*One implant costs £2605. A total of 27 implants were used in 21 patients (6 patients had two levels) giving a mean cost of 3,349 per patient. **Range excluding device cost.

The incremental cost for the X-Stop was 2,437, and the incremental QALY was -0.11. These values were inputted in the formula to calculate the incremental cost effectiveness ratio (ICER).

$$\text{ICER} = \frac{\text{Total cost of X-Stop} - \text{Total cost of Laminectomy}}{\text{QALY X-Stop} - \text{QALY laminectomy}}$$

$$\text{QALY X-Stop} - \text{QALY laminectomy}$$

ICER = (5,148 – 2,711) / (0.81-0.92) = -22,247.27. On average, the X-Stop had a lower gain in QALY and was also costlier than a laminectomy. This therefore results in a negative ICER which places the X-Stop on the North-West corner of the cost-effectiveness plane with QALY loss for increased cost. (Fig.11) If the cost of the device is removed from the equation, the incremental cost of the X-Stop would be -912.8 and the ICER would then be £8,290.9.

If the cost of the four re-operations for removal of X-Stop and decompression are factored in then the average additional cost for the second surgery and admission would be £3,147.35, which increases the average cost of the X-Stop from £5,148 to £5,747. There was one re-operation in the laminectomy group that cost an additional £3,442.71 (£1,511 theatre time and £1,931.71 cost of admission). This increases the average cost of a laminectomy from £2,711 to £2,844. The effects of this are demonstrated in the sensitivity analysis on page 83.

EQ5D – Health status

The mean pre-operative Health status score on the VAS scale of the EQ5D was 52.6% for the X-Stop group and 66.6% for the Laminectomy group. After two years, the mean scores were 58% for the X-Stop group and 57.9% in

the laminectomy group. None of these changes were statistically significant. (*P*-value X-stop 0.50 and laminectomy 0.43).

If the results of those five patients who crossed over from the X-Stop arm to the laminectomy arm are considered within the laminectomy group (as-treated analysis) then the results after two years would be an improvement of 8.57% for the X-Stop group (54.64% pre-op to 63.21% post-op *P*-value = 0.42) and a deterioration of 3.18% for the laminectomy group (57.27% pre-op to 54.01% *P*-value 0.46).

Secondary Outcomes

SF36

SF-36 Score	Laminectomy Group					X- Stop Group				
	Preop	6 Mts	1 Yr	2 Yrs	Treatment effect (SE)	Preop	6 Mts	1 Yr	2 Yrs	Treatment effect (SE)
PF	26.3	41.8	41.8	36.9	+8.3(5.1)	22.5	42.3	47.9	43.7	+15(8.3)
RP	22.0	38.6	31.6	14.7	-12.5(10.5)	13.2	37.5	55.4	35.3	+21.3(11.0)
BP	30.0	42.2	43.7	43.5	-10.3(6.2)	24.9	42.6	51.0	39.1	+17.6(9.2)
GH	57.0	55.3	52.2	49.9	-5.5(4.3)	55.9	53.0	56.6	49.5	-0.2(8.9)
VT	45.4	49.1	45.5	54.7	+3.3(6.1)	39.2	49.5	59.3	50	+2.8(6.7)
SF	56.5	63.1	58.6	65.4	+4.2(7.2)	37.5	51.9	65.2	54.4	+21.1(11.4)
RE	52.0	53.1	59.6	49.0	+9.2(12.3)	35	51.7	69.0	54.9	+12.5(14.2)
MH	67.5	67.5	68.8	74.1	+6.5(5.1)	57.5	66.8	77.4	67.5	+1.3(4.9)

Table 8 – Results of the SF36 scores for the two surgical arms at baseline and at the three post-operative time intervals. *PF* – physical functioning, *RP* – role physical, *BP* – bodily pain, *GH* –general health, *VT* – vitality, *SF* – social functioning, *RE* – role emotional, *MH* – mental health, *PCS* – physical component summary, *MCS* – mental component summary.

Pre- and Post-treatment mean SF-36 scores

The table above (Table 8) demonstrates the mean score for all the SF36 domains. The Paired Wilcoxon signed-rank test was used to calculate treatment effect. This was done for both intention to treat analysis and as-treated analysis. The table below (Table 9) shows the overall effective change with both types of analysis.

SF36 domains	Laminectomy ITT(SE)	Laminectomy AT (SE)	X-Stop ITT (SE)	X-Stop AT (SE)
Physical function	8.3(5.1)	7.6 (4.3)	15(8.3)	19.5 (11.5)
Role Physical	-12.5(10.5)	-7.6 (9.2)	21.3 (11.0)	26.3 (13.9)
Bodily Pain	-10.3(6.2)	14.1 (5.7)*	17.6 (9.2)	12.9 (12.1)
General Health	-5.5(4.3)	-8.7 (3.8)*	-0.2 (8.9)	9 (11.9)
Vitality	3.3(6.1)	3.2 (4.9)	2.8 (6.7)	2.7 (9.4)
Social Functioning	4.2(7.2)	5 (7.5)	21.1 (11.4)	27.8 (12.4)*
Role Emotional	9.2(12.3)	13 (10.4)	12.5 (14.2)	6.1 (19.0)
Mental Health	6.5(5.1)	6.3 (4.0)	1.3 (4.9)	-0.73 (7.1)

Table 9 – Effective change between baseline and two years for both Intention to Treat (ITT) and As-Treated (AT).

***Statistically significant**

When the as-treated analysis is considered, the laminectomy patients do significantly worse for the domains of bodily pain and general health whereas the X-Stop group perform significantly better in social functioning.

Disease Specific Questionnaires

Quebec Back Pain Disability Score

Intention to Treat Analysis

X-Stop – The mean pre-operative score was 64.75% vs mean postoperative score at 24 months was 48.27%. This is a mean improvement of 16 points ($p=0.05$). The minimal clinically important difference for QBPDS in chronic conditions is 9 points.

Laminectomy – The mean pre-operative score was 58.77% vs mean postoperative score at 24 months was 55.88%. ($p=0.65$).

As-treated Analysis

X-Stop – Pre-op mean 65.77% vs 24 months mean 50.07% – ($p=0.15$).

Laminectomy – Pre-op mean 59.50% vs 24 months mean 53.20% - ($p=0.28$).

Oswestry Disability Index (ODI)

The mean pre-operative score for the X-Stop patients was 49.37 and 40.75 for Laminectomy. A lower score on the ODI signifies less disability and therefore a better outcome. The minimum detectable change with clinical significance is 10% of points (90% confidence).^{cliv} A change of less than this may be attributable to error in the measurement.

		<u>Post op Score (SE) - % change from pre-op</u>
<i>Oswestry Disability Index - 6 months (0 to 100%)</i>	Laminectomy	36.55 (5.22) - 9.51%
	X-Stop	38.64 (4.55) - <u>10.74%</u>
<i>Oswestry Disability Index - 12 months (0 to 100%)</i>	Laminectomy	41.23 (4.32) - 7.39%
	X-Stop	34.62 (7.02) - <u>15.5%</u>
<i>Oswestry Disability Index - 2 years (0 to 100%)</i>	Laminectomy	41.96 (5.50) - -1.21%
	X-Stop	41.68 (5.96) - 7.77%

Table 10 – ODI outcome scores at 6 months, 12 months and two years and percentage change from baseline.

With intention to treat analysis, the ODI scores showed an initial improvement for the laminectomy group however deteriorated and were worse than the pre-operative scores at two years (-1.21%). For the X-Stop group there was a significant improvement at 6 months (10.74%) and 12 months (15.5%). At two years, there was an improvement of 7.77% compared to pre-op however this did not reach the minimum detectable change of 10%.

As-treated Analysis for ODI questionnaire

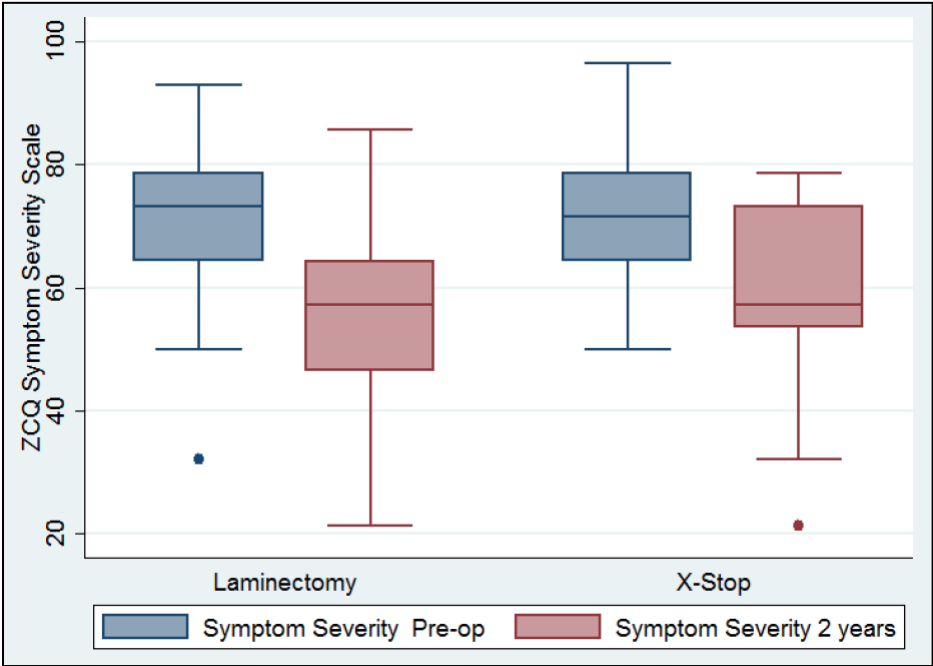
The X-Stop pre-op mean score was 49.2% vs 41.87% at 24 months (SE 7.73) – mean difference 7.34% ($p = 0.37$). The Laminectomy pre-op mean score was 42.71% vs 41.73% at 24 months (SE 3.9) – mean difference 0.98% ($p = 0.83$). Therefore, the ODI questionnaire showed similar results for both the as-treated analysis and intention-to-treat analysis.

Zurich Claudication Questionnaire (ZCQ)

The ZCQ score also increases with worsening disability. The difference in the mean score between baseline and 24 months for the X-Stop group was considerable but not statistically significant for the symptom severity domain (73.01 pre-op vs 58.72 at 24 months, $p=0.07$) but significant for the physical functioning domain of the ZCQ (67.01 pre-op vs 53.81 at 24 months, $p=0.007$). For the laminectomy arm, although the mean difference was similar to the

X-Stop group, this did reach statistical significance for the symptom severity domain (69.84 pre-op vs 55.76, $p=0.0002$). However, the physical functioning domain was not significantly different between baseline and 24 months (55.22 pre-op vs 53.81 at 24 months, $p=0.78$). (Fig. 20)

A)



B)

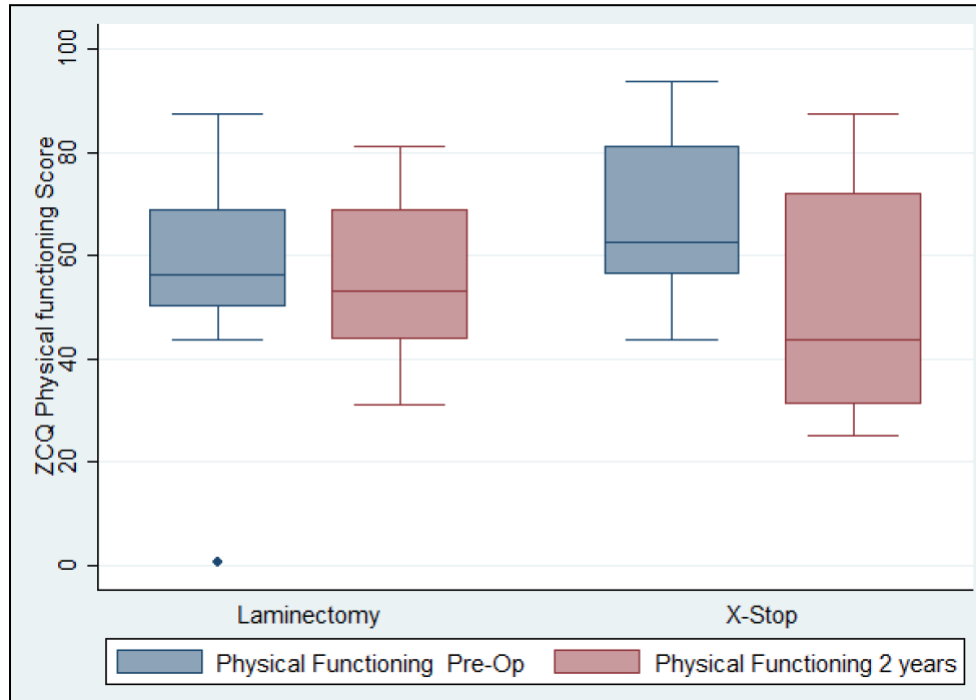


Figure 20 – Zurich Claudication Questionnaire (ZCQ): A) Symptom Severity Score and B) Physical Functioning – Pre-operative scores and scores at two years post operatively. (ZCQ score increases with disability). Improvement was seen in both groups. This was statistically significant in the laminectomy group for the Symptom Severity domain ($P=0.0002$) and for the X-Stop group in the Physical Functioning domain ($P=0.007$).

As-treated Analysis

ZCQ symptom severity score – X-Stop – improvement of 17.31 (75.82 pre vs 58.51 24 months) $p = 0.01$

ZCQ symptom severity score – Laminectomy - improvement of 12.41 (68.9 pre vs 56.5 24 months) $p = 0.0002^*$

ZCQ physical functioning score – X-Stop – improvement of 14.4 (69.23 pre vs 54.8 24 months) $p = 0.03^*$

ZCQ physical functioning score – Laminectomy – improvement of 3.2 (56.5 pre vs 53.26 24 months) $p = 0.43$

Satisfaction score – X-Stop 24 months – mean 51.66%

Satisfaction score – Laminectomy 24 months – mean 58.15%

The As-treated analysis also show a significant improvement in the symptom severity domain for the laminectomy group ($P=0.01$) and in the physical functioning domain for the X-Stop group ($P=0.03$).

Summary of Questionnaire Results at Two years.

A) Intention to Treat Analysis

	Laminectomy	X-Stop
EQ5D TTO score	Significant improvement	No significant difference
EQ5D Health status	No significant difference	No significant difference
SF36	Improved in 5 out of 8 domains	Improved in 7 out of 8 domains
QBPDS	No significant difference	Significant improvement
ODI	No significant difference	No significant difference
ZCQ Symptom severity	Significant improvement	No significant difference
ZCQ Physical functioning	No significant difference	Significant improvement

B) As-Treated Analysis

	Laminectomy	X-Stop
EQ5D TTO score	Significant improvement	Significant improvement
EQ5D Health status	No significant difference	No significant difference
SF36	Improved in 6 out of 8 domains	Improved in 7 out of 8 domains
QBPDS	No significant difference	Significant improvement
ODI	No significant improvement	No significant difference
ZCQ Symptom severity	Significant improvement	Significant improvement
ZCQ Physical functioning	No significant difference	Significant improvement

Table 11 – Summary of results of all the PROMS in the CELAX trial with intention-to-treat A) and As-treated analyses B).
 statistically significant improvement no significant difference

Predictors of outcome

Multivariable analysis was carried out to look for association of certain predictor variables with outcome. The effect of demographics and pre-operative factors on quality of life was analysed: age, gender, presence of

spondylolisthesis, presence of co-morbidities and whether re-operations occurred. The outcome variable used was the difference in EQ5D score between baseline and at two years. The best fitting regression model is shown here:

Difference in EQ5D TTO score between baseline and at 24 months	Co-efficient	P value	95% confidence interval	
Age	.0061553	0.303	.000025	.0198586
Operation (X-Stop or Laminectomy)	-.0308206	0.774	-.3490565	.0784089
Presence of Co-morbidities	.1092433	0.330	-.6841699	-.1501602
Re-operation	-.3491125	0.035	-.1227819	.2386403

Table 12 – Best fitting regression model using change in EQ5D scores as the dependent variable. R-squared = 0.15

The difference in EQ5D scores at 24 months were significantly predicted by whether the patient was re-operated. This predictor variable had a negative effect on quality of life. The type of operation (X-Stop or Laminectomy) did not have a significant prediction value. Having an X-Stop insertion could potentially negatively affect the outcome score by 0.03 but this association was very weak (confidence interval included zero).

Sensitivity Analysis

	Description	Mean Cost (difference)	Mean QALY (difference)
As-treated analysis	5 crossovers from X-stop to laminectomy	X-Stop £4,941.98 (-205.94) Laminectomy £2670.92 (-40.89)	X-Stop 0.86 (+0.06) Laminectomy 0.87 (-0.04)
Without cost of device	£2,605 per device	X-Stop £1,798 (-3,349) Laminectomy N/A	/
Without outliers	1 extended stay in X-stop, 3 in laminectomy arm	X-Stop £4,995 (-153) Laminectomy £2,520 (-191)	X-Stop 0.87 (+0.06) Laminectomy 0.95 (+0.03)
With cost of re-operations	4 X-Stop removals 1 laminectomy re-operated for CSF leak	X-Stop £5,747 (+599) Laminectomy £2,844.29 (+132.49)	/

Table 13 – Effects on cost and QALY by using As-treated analysis instead of intention-to-treat, excluding cost of the X-Stop device, removing outliers with extended length of stay and including the cost of re-operations.

Effect of Outliers

In the X-Stop group there was one patient who stayed in hospital for 20 days due to severe back pain post-operatively. If this outlier is removed from the analysis, then the mean cost of stay for the X-Stop group would go down from £686.92 to £533.11. The mean total cost would then be £1,646.85 for the X-Stop group (without the device) and £2,711.8 for the laminectomy group. (Table 13)

Re-operations

EQ5D TTO score	Baseline	6 months	12 months	24 months
1	-0.074	-0.349	-0.126	-0.126
2	0.088	-0.239	-0.239	-0.181
3	0.62	0.727	0.796	0.796
4	0.62	0.26	0.189	0.189

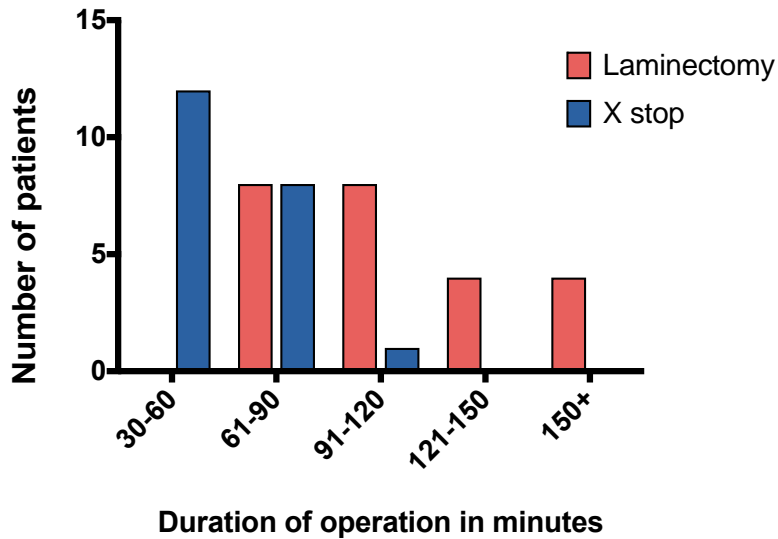
Table 14 – EQ5D TTO scores of the four patients who had an X-Stop inserted and then removed after 1 - 12 months, 2 – 6 months, 3 - 8 months and 4 - 12 months. –
The shaded boxes represent the scores after the X-Stop was removed.

Table 14 shows the EQ5D scores of the four X-Stop patients who crossed over to the laminectomy arm due to failure of the X-Stop to improve symptoms. The data from these patients was added to the laminectomy group when calculating the ‘as-treated’ analysis. The scores after the X-Stop was removed and a laminectomy was carried out are similar to the scores before the re-operation in all four patients. The quality of life of three out of the four patients (patient 1,2 and 4) deteriorated compared to baseline. Patient 3 improved marginally at two years. This means that despite having a laminectomy, these patients still didn’t improve. Patient 1 had a two level X-Stop whilst the other three were all single level. None of these four patients had spondylolisthesis. All four patients had bilateral leg pain pre-operatively. Patient 1,3 and 4 also had pre-operative back pain. Patient 3 also had pre-operative leg numbness.

Grade of Surgeon

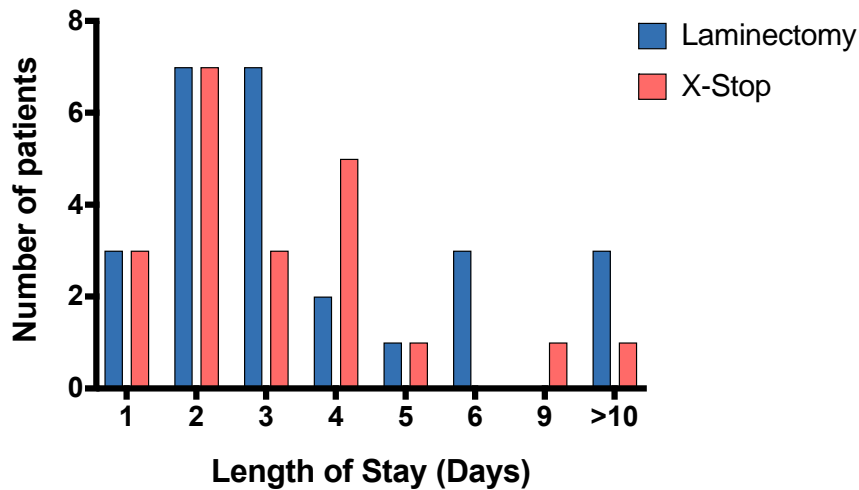
Operation	Surgeon		Total
	Registrar	Consultant	
Laminectomy	18	8	26
X-Stop	5	16	21
Total	23	24	47

Most X-Stop insertions were carried out by a consultant (76%) whereas most laminectomies were carried out by registrars (69%). The mean length of an operation carried out by a consultant was 81 minutes vs 110 minutes if carried out by a registrar. However, since laminectomies had a longer operation time than an X-Stop insertion, it is expected that the mean operative time would be longer for registrars. There were 5 complications when a registrar was performing the operation whereas consultants had three complications.

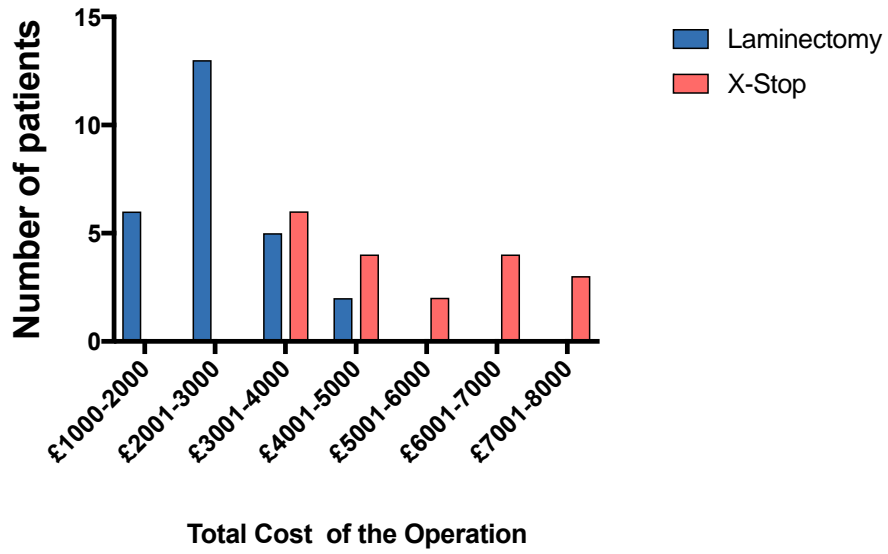


A)

*The difference between the mean duration of laminectomy versus X-Stop was significantly different at $P < 0.05$ ($p = 0.0014$). Wilcoxon rank test.



B)



c)

Figure 21 – Comparison of A) Operative time, B) Length of Stay and C) Total cost between the two surgical arms, Laminectomy and X-Stop.

Discussion

Over recent years, interest in the economic evaluation of healthcare has risen and more studies are looking not just at the clinical effect of treatment but also its economic burden and financial feasibility. The economic importance of the question that this study aims to answer is undisputed since LSS is becoming more prevalent due to increasing life expectancy. The results of this study are relevant to the choice being faced by decision makers and has resource implications.

When a new treatment option becomes available, which has a similar effect as the standard treatment that is in current practice, then, all things being equal, it would make sense to choose the cheapest option. The benefits of the different treatments, as well as the cost, often differ however. This process of comparison is called cost-effectiveness analysis. The average cost for a patient undergoing a laminectomy was £2,711.8 and for having an X-Stop insertion was £5,148. Removing the cost of the X-Stop device from the cost calculations resulted in the X-Stop being cheaper than a laminectomy mainly due to shorter operating times. (Table 13)

The cost of surgery varied significantly between the different centres. A market force factor exists for every trust in the UK and this is applied when costings for reimbursement are being calculated. For Centre 1 the market force factor was 1.2976, for Centre 2 it was 1.2125 and for Centre 3 this was 1.0744. This means that procedures cost more in Centre 1 which is in central London compared to the other centres. One strong point of this study is that both the resources (operating theatre time and days of hospital stay) and their prices (unit costs) are stated. As mentioned in the methods section, the total theatre time and length of stay were deemed to be a more accurate way of measuring true hospital costs rather than through the reimbursement method using HRGs or PLICS. This is because what hospitals charge for the service they provide differs significantly from the money they spend on carrying out the service. In addition, there was a significant variability in the way the three centres receive their reimbursement as well as a difference in the price due to the market force factor. The latter was accounted for in the cost per minute and cost per day used to calculate the total cost.

Only direct costs were measured in the CELAX trial. Indirect costs such as time off work, GP visits and cost of supplemental long term analgesia were not included as it is impossible to capture such data accurately and unlikely to have a significant bearing on the trial conclusions.

The results suggest that lumbar laminectomy is more cost-effective than insertion of the X-Stop for treatment of LSS. The main reason for this is due to the difference in price of the device rather than clinical effectiveness. With both the intention to treat analysis and as-treated analysis, the X-Stop patients showed improved outcome in all the PROMS. However, if the costs of the re-operations are included the cost-effectiveness of the X-Stop will be even more reduced. A negative ICER was obtained (-22,247.27). This can mean either that the new treatment

proposed is cheaper (cost savings) or, as in the case of this study, that the new treatment proposed has a negative health outcome. Compared to previously published cost-effectiveness studies, the cost of theatre time in the UK is similar to other European countries (approx. 12 euros per minute)^{clv}

The results from this study build on previous studies on LSS. Both groups improved overall with surgery and maintained this improvement for two years. The overall complication rate was 14.89% which is similar to that quoted in the literature (12% in the SPORT trial). This rate is a slight overestimate as it includes a break in the spinous process of a patient randomised to receiving the device. It is also one of the reasons why an X-Stop insertion is done under a general anaesthetic to allow conversion to a laminectomy if necessary. Converting the operation to a laminectomy could, however, have increased the length of stay as this patient was discharged home the next day rather than that same day. Most of the X-Stop patients did however, end up being admitted longer than anticipated and often spent at least one night in hospital anyway. The reason for this was mainly for physiotherapy assessment and advice which happened on the following day. There is also a culture of observing patients for 24 hours after surgery especially in centres where the use of the X-Stop was not familiar.

Factors affecting outcome

Pre-operative status; Although the patients were randomly allocated to one of the two surgical arms, the X-Stop group had a higher prevalence of grade 1 spondylolisthesis (5 vs 1). The pre-operative questionnaires did not show any statistically significant difference between the two groups however, the EQ5D TTO and VAS scores were slightly worse for the X-Stop group. Multiple regression analysis did not detect a significant effect on the difference in EQ5D scores with the presence of spondylolisthesis and none of the pre-operative symptoms (back pain, leg pain or numbness) had a significant predictive value on the two-year outcome score either.

Variability in surgeon' experience; More than half of the operations were carried out by a consultant (24/47), however there was a higher proportion of consultants present during an X-Stop insertion as compared to a laminectomy (16/21 of X-Stops and 8/26 of laminectomies). This was because the X-Stop is a relatively new device with not many centres having the experience of using it. A laminectomy, on the other hand, is performed in every neurosurgical department and is often one of the first operations that a junior trainee starts practicing independently. As a result, a consultant was only present in 8 of the 26 laminectomies. Experience of the operating surgeon is important and is associated with less complications. This could have had an influence on the higher complication rate seen in the laminectomy group.

The length of stay in hospital was not significantly different between the two groups. This was a surprising result since the main advantage of the X-Stop is the relatively shorter operation time and minimal invasiveness that ought to require less convalescence and therefore making it a cheaper option in this regard. Ten out of the 21 cases who received an X-stop went home on the day or the following day after surgery. However, the rest had a

longer length of stay with one case having stayed for a total of 20 days due to increased back pain immediately post op. This required investigation with X-rays and CT scan of the lumbar spine and even a trial of injections. For this reason, the costs of the X-Stop remained high which in addition to the cost of the device led to a lesser cost-effectiveness. In the laminectomy group, there were three patients who also had an unanticipated longer length of stay. In all three cases this was due to complications from the surgery (1 myocardial infarction and 2 CSF leaks).

There was a mix of results amongst the various patient rated outcome measures. For instance, the EQ5D showed significant improvement in the laminectomy group whereas the SF36 showed a significant deterioration in the laminectomy group. This is likely to be due to the different aspects that these instruments are designed to measure. The EQ5D questionnaire specifically asks about mobility and depression whereas the SF36 asks more general health perception questions. This dissimilarity was also seen with the disease specific questionnaires. There was significant improvement in the X-Stop group of patients for all the three questionnaires, however this only reached statistical significance with the QBPDS and the physical functioning domain of the ZCQ. The laminectomy score showed a deterioration in the ODI scores at two years but this was not significant. A significant improvement was detected by the symptom severity score of the ZCQ. This substantiates the argument that the operations had similar clinical outcomes.

Challenges

The main challenge that this trial faced was with recruitment. Most eligible patients did not like the idea of randomisation and wanted to choose one of the two operations. Most of the time patients favoured the X-Stop device as they perceived it to be a more modern and less invasive operation with the same outcome. Other issues included availability of the device in certain centres. In Centre 3 the device was only available as part of the study and therefore was not kept on the shelf like in the two other centres. Another impact on recruitment was that Centre 3 closed during the study period and was amalgamated with a bigger trust. During the transition phase, this centre stopped receiving GP referrals and thus screening for new patients was no longer possible. Adding new NHS centres proved difficult as most did no longer offer the device due to its expense. It was also noted that several spine surgeons were not keen to join the trial since they fell out of favour with the X-Stop. This was because they have experienced failures where they had to remove the device and carry out a laminectomy. Since the X-Stop device is reversible (i.e. can be removed) and minimally invasive, unlike a laminectomy, many surgeons have tried it in situations where they would not have otherwise offered surgery for instance when back pain was the predominant symptom and when no claudicant features were present. This unsurprisingly did not have favourable clinical outcomes. This together with its cost has led to the device falling out of fashion. Another reason why the X-Stop might appear to be at a disadvantage compared to a laminectomy is its reversibility. With either operation, it is unlikely that all symptoms will vanish immediately and completely after surgery, in fact symptoms are not infrequently worse in the immediate post-operative period. However, since with the X-Stop there is the option of it being removed and 'trying out' a laminectomy instead, this gives the surgeons the option

of calling it a failed operation. On the other hand, after a laminectomy, unless there is the presence of a post op haematoma, CSF leak or infection, patients are often reassured and sent for physiotherapy and pain clinic reviews. A laminectomy cannot be reversed so it is less commonly labelled as a failed operation by surgeons.

Another challenge faced whilst conducting this study was the issue with compliance of data collection. Patients often commented about the length and repetitiveness of the questionnaires especially with the SF36. Questionnaires were completed either during follow up visits, over the phone or by returned by post. Postal questionnaires were sometimes filled inaccurately or certain questions missed and left blank. The most commonly skipped question was section 8 of the ODI score which concerned the impact of back pain on the patients' sex life. The recommended correction for this was applied to the scoring system.

Loss of follow up was high due to illness unrelated to LSS. There were three deaths within a year from surgery. This is not unexpected since LSS affects mainly the elderly. This loss to follow up was higher than that reported in other studies comparing the X-Stop to laminectomy, mainly because the follow up in other studies was only for one year.^{clvi}

Certain issues arise when using PROMS. The scores may be affected by patients' perception on the day of questioning. Other co-morbidities acquired during the length of the study that are unrelated to the operation can affect the way a patient answers the questions. Especially if these affected mobility, for example stroke resulting in a hemiparesis.

Whether the effects recorded in the study extend after the trial period is an interesting question. Removal of the X-Stop device and converting to laminectomy occurred in 4 patients within the study period. This happened throughout the two years (8 months, one year, two years). It is likely that some of the patients who had an X-Stop inserted may have been re-operated on after the study period. The longevity for both operations is unknown. Patients may develop LSS at other levels and develop other comorbidities with age, therefore extended follow up may still not be informative on the durability of the effects of surgery.

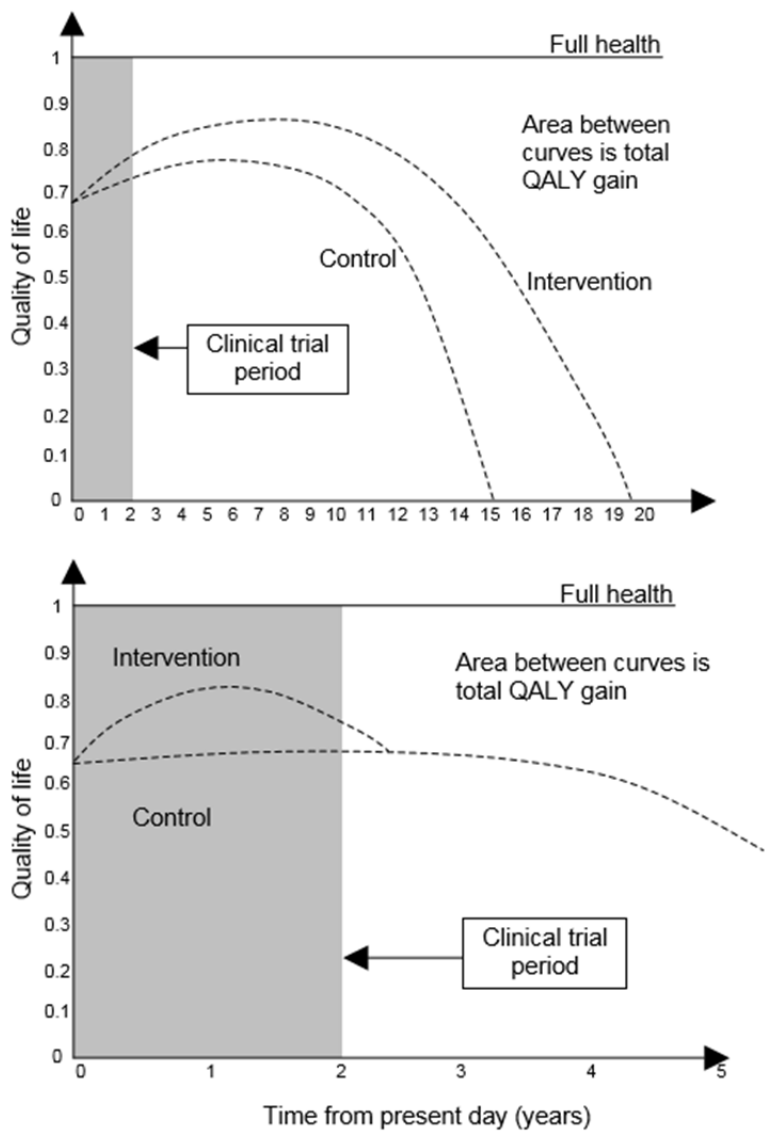


Figure 22 - from Edwards et al - QALY profile for RCTs where health gain is long term vs short term

The treatment of LSS has no effect on life expectancy, but it does have an effect on quality of life. This treatment effect is also known to be short-term and the quality of life over time curve will eventually cross the control or “no treatment” curve. (Figure 22) By measuring quality of life at various time points during the study period, one can extrapolate and therefore predict when this will happen. In the CELAX trial, the improvement in quality of life from baseline was maintained at the two-year time point for both treatment arms. (Figure 18) However, whilst the laminectomy group of patients maintained a steady increase over the study period, the X-Stop patients plateaued

at six months. The CELAX trial did not include a control arm with no surgical treatment and therefore the true effect of surgery cannot be known.

Strengths of the study

This was a prospective randomised control trial which meant that the two groups were directly comparable, thus eliminating selection bias. The two population groups only differed by the intervention that they received. The trial included three centres and therefore this allowed for the variability between hospitals and between different surgeons to be reflected in the results thus giving a truer representation of the NHS. There was variability in the grade of surgeons like there normally is in the NHS as well as variability in costs. The study had well balanced groups with similar demographics, symptom severity scores and radiological findings.

The statistical analysis and sample size were estimated from the outset. Intention to treat analysis was used. This is regarded as a controversial topic in statistics. Intention to treat analysis includes all randomised patients in the group to which they were assigned regardless of the treatment that they actually received. This type of analysis disregards what happens after randomisation and ignores non-compliance and protocol deviations. This is meant to be a truer representation of clinical practice. Intention to treat analysis also accounts for missing outcomes which is a common problem in RCTs. The argument against this type of analyses is that the outcomes reported may not be attributed to the treatment received and this makes interpretation difficult especially if subjects cross over into the other treatment group. In the CELAX trial, patients from the X-Stop arm could cross over to the laminectomy arm but the reverse was not possible. Once a patient has undergone a laminectomy they can no longer have an X-stop inserted. In the trial, there were two patients who were randomised to an X-stop but never received it. In one case the device was not available and the patient withdrew from the study. In the other case, the spinous process at the operating level broke off and therefore the procedure had to be converted to a laminectomy. There were four patients who had their X-Stop removed and underwent a laminectomy. The statistical analysis was carried out both with the intention to treat method as well as with the actual procedure received. For both analyses the patients receiving a laminectomy showed a statistically significant improvement at 2 years. The patients receiving an X-Stop showed no significant difference at two years with both the intention to treat analysis and with the repeat analysis with the 5 patients removed from the group. However, the mean score at two years improved from 0.48 to 0.53. Whereas for the laminectomy group, the mean score at two years deteriorated when the 6 patients who were randomised to an X-Stop were added to the analysis (0.57 to 0.53).

Patient rated outcome measures were used. These have the advantage of removing investigator bias as the patient themselves fill out the questionnaires. Having a different range of questionnaires, both disease specific and general, helps to cancel out effects from other co-morbidities that are not related to LSS.

Highlighted case

ME presented with bilateral claudicant leg pain and underwent X-Stop insertion at the L4/5 level with a size 10mm implant. This resulted in worsening of the symptoms immediately post operatively that led to a prolonged length of stay of 20 days. The back pain was reported to be much worse and the patient was also experiencing severe nausea. A post-operative MRI and hip x-rays were obtained. The imaging revealed good positioning of the X-stop with no concerning appearances. A review by the pain team was also necessary for symptom control. There was no symptom improvement and therefore the IDD was removed after six months and a lumbar decompression carried out in the same sitting. On reviewing the reported outcome measures specifically for this case, the scores over two years were as follows:

	Pre-op Baseline	6 months	12 months	24 months
Quality of Life				
EQ5D	21232	22333	22333	22233
TTO score	0.088	-0.239	-0.239	-0.181
Health status	40	50	50	50
SF36 Physical functioning	30%	5%	5%	10%
SF36 General Health	60%	12%	25%	30%
Disease Specific				
QBPDS	69.5%	83%	83%	12.5%
ODI	57.8%	68.88%	68.88%	60%
ZCQ Symptom Severity	60.71%	75%	75%	78.57%
ZCQ Physical function scale	62.5%	81.25%	81.25%	68.75%
ZCQ Patient satisfaction	n/a	100%	100%	100%

Table 15 - Questionnaire scores for the highlighted case of a failed X-Stop insertion requiring removal and laminectomy after six months.

The second operation took place just after the 6 months' scores were obtained. Therefore, the 12 month scores were obtained six months after the laminectomy and X-Stop removal. The scores are almost identical between 6 months and 12 months except for a slight improvement in the general health perception score of the SF36 questionnaire. Two years after the initial operation, the back-pain score improved significantly however, there was only minimal improvement in the physical functioning scores and there was worsening of the symptom severity scores. The patient remained very dissatisfied with the overall outcome (ZCQ satisfaction score 100%).

This case demonstrates that LSS can be a very difficult condition to treat. Patients who had their IDD removed and subsequently underwent a laminectomy are an interesting cohort to study clinical efficacy. This subset of patients inadvertently received both operations and therefore the outcomes after the second operation (laminectomy) can be compared to the outcomes after the IDD was inserted. It was noted that those patients whose symptoms did not improve with the IDD, did not improve after the laminectomy either. This demonstrates that symptoms of LSS may not resolve despite adequate decompression. The reason for this is postulated to be due to the multifactorial degenerative changes in the spine that cannot be reversed with surgery.

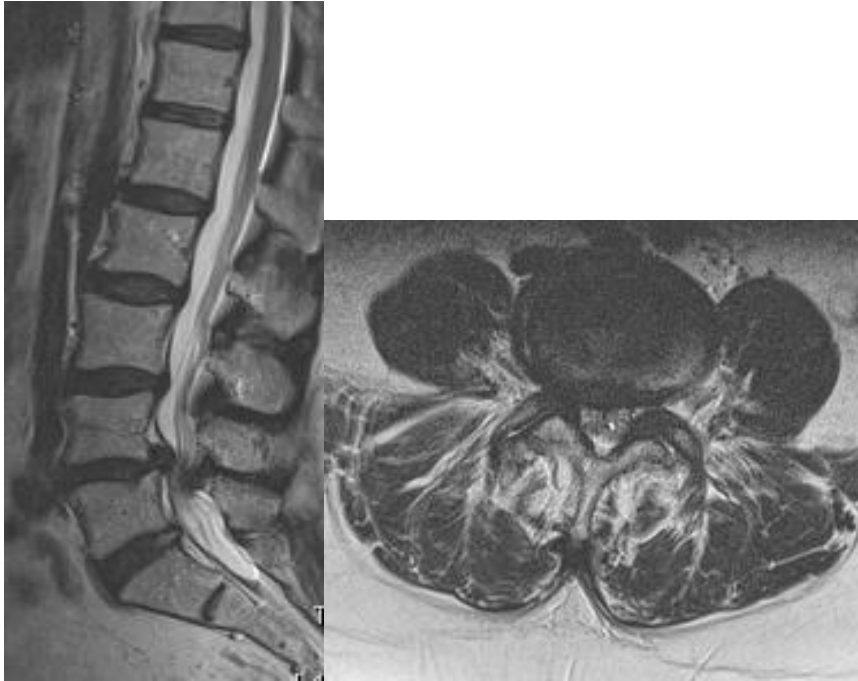


Figure 23 - Pre-operative MRI scan of the lumbar spine. Sagittal T2 images and axial T2 images through the stenotic L4/5 level.



Figure 24 - Post-operative MRI scan T2 sagittal A) and axial B) with X-Stop in situ. Lateral X-ray of the lumbar spine flexion C) and extension D) with X-Stop in situ.

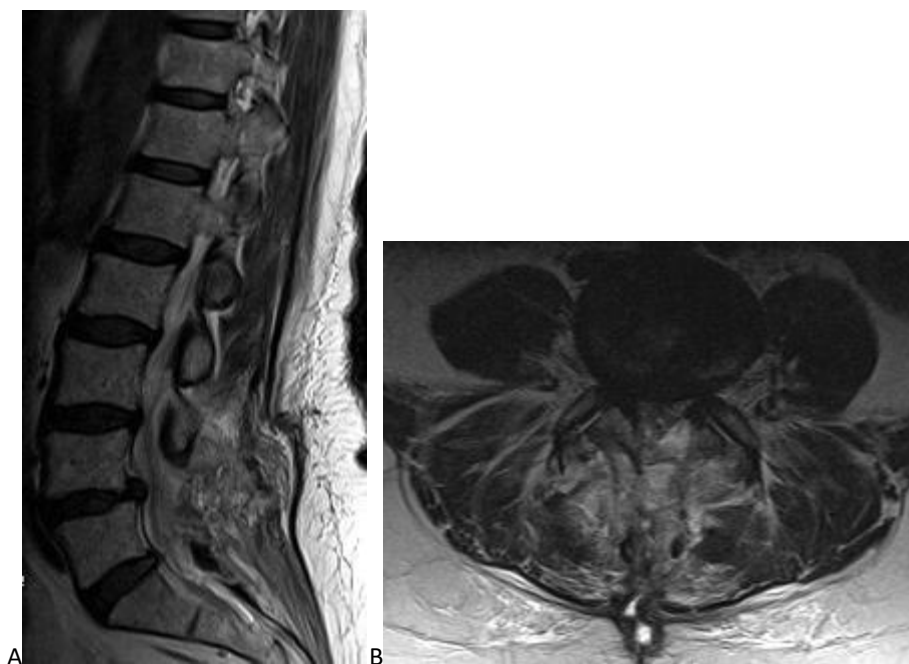


Figure 25 - MRI of the lumbar spine after X-Stop removal and laminectomy at L4/5 level. A) T2 sagittal B) T2 axial through the decompressed level.

Drawbacks of Randomised Control Trials

When attempting to get a trial up and running one faces many obstacles which can hinder and even altogether stop the research from taking off. Initially there is the issue of funding, obtaining ethics approval and setting up the trial protocols in the various centres. Then there is the challenge of recruitment, establishing protected research time, allocating supporting research staff and getting through the vast amount of paperwork. It is estimated that only 50% of RCT's hit their recruitment target.^{clvii} These challenges can undermine the power of the study and can jeopardise the success of the trial altogether.

Not infrequently one encounters clinical situations where the choice of management is unclear and where the literature is divided as to what course one should pursue. Clinical trials aim to resolve this issue by attempting to answer such controversial questions. However, despite the lack of clinical evidence, many practitioners feel strongly one way or another and do not buy into the idea of randomly allocating their patients to a trial arm which they do not agree with. Many doctors admitted of having a "hunch" as to what the better treatment should be.^{clviii} Recruitment therefore suffers due to this lack of eagerness by some of the investigators even though they had initially agreed to participate. Due to these problems with recruitment clinical trials may lead to inconclusive results which are not generalizable.

The size of the trial is reflected in the number of patients required to demonstrate a scientifically valid conclusion. In general, the larger the sample size the more confidence one has in the results and the higher the power of the

study. However, this is generally determined by the population being studied and by the size of the effect that the intervention has. A small sample size is sensitive to outliers and the data can be easily skewed. Unless the effect of the intervention is large it is difficult to obtain a significant result. For this reason, sensitivity analysis was carried out in the CELAX trial to ensure that removing outliers does not lead to significantly different results. The sensitivity analysis showed that removing the cost of the device would change the ICER from -£22,247.27 to £8,290.9.

Randomised control trials are an imperfect way of conducting research however, randomisation remains the best method available for establishing treatment effects. One needs to interpret results with caution and consider their limitations before adopting the conclusions into clinical practice.

Conclusion

The data from the CELAX study supports the following conclusions:

Both a decompressive lumbar Laminectomy and insertion of the X-Stop interspinous distraction device are clinically effective options in the surgical management of LSS. A decompressive laminectomy resulted in better clinical outcomes and was significantly cheaper than an X-Stop insertion therefore, it was the more cost-effective option. However, it resulted in a higher complication rate than an X-Stop insertion.

Those patients who did not improve with an X-Stop insertion did not improve after a laminectomy either implying that there are some patients who simply do not respond to treatment.

The X-Stop IDD is an option for LSS in patients with high risk co-morbidities due to shorter operating times and less risk of complications.

Clinical outcomes are similar to a Laminectomy but the procedure is less cost effective mainly due to the cost of the device.

The results from the study may contribute to the NICE guidelines on the use of IDDs as second line to laminectomy when the latter is contra-indicated.

Acknowledgements

The CELAX trial was supported by a grant from UCLH contingency fund amounting to £25,000.

The CELAX trial also received financial support from Medtronic Inc. between 2008 and 2010.

This thesis was independent of other work. No other thesis was accessed during the writing of this thesis.

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Appendix

CASE REPORT FORMS

Version 1.0

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CASE REPORT FORM (CRF 1)

**Please complete in block
capitals and in black ink**

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PATIENT SELECTION

Inclusion Criteria

- is a male or non-pregnant female patients
- is aged between 18-80 years (inclusive)
- has a BMI <35 kg/m²
- has a preoperative ODI>30 points and a ZCQ-Physical Function Domain > 2
- has chronic leg pain with or without back pain of greater than 6 months duration improved by flexion, and who are suitable candidates for posterior lumbar surgery
- has completed at least 6 months of conservative treatment without obtaining adequate symptomatic relief
- has degenerative changes at 1 or 2 adjacent levels between L1-S1 confirmed by X-Ray, CT or MRI scan with one or more of the following:
- is physically and mentally willing and able to comply with the postoperative scheduled clinical and radiographic evaluations.
- none of the above

Exclusion Criteria

- fixed motor deficit
- is skeletally immature
- has undergone previous lumbar spinal surgery which could affect the trial outcome (e.g., disc replacement)
- has obvious signs of psychological^{clix} or worker compensation or litigation claims elements to their condition
- is unwilling or unable to give consent or adhere to the follow-up programme
- has active infection or metastatic disease
- has non-degenerative spondylolisthesis
- has degenerative spondylolisthesis \geq Meyerding Grade 2
- has a known allergy to implant materials
- has severe osteoporosis or rheumatoid arthritis
- cauda equina syndrome
- none of the above

ELIGIBLE/ NON-ELIGIBLE (please circle one)

COST EFFECTIVENESS OF LUMBAR LAMINECTOMY VS XSTOP

CASE REPORT FORM (CRF 2)

Please complete in block capitals and in black ink

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

EPIDEMIOLOGICAL/DEMOGRAPHIC DATA

DOB: ____/____/____

AGE:

GENDER: Male Female

ETHNICITY: Afro-Caribbean White (British)

Asian White (Other)

Middle Eastern Oriental

JOB: _____

OTHER MH: _____

EPIDURAL INJECTION: YES NO

If YES: Date(s) _____

MEDICATION:

ASA SCORE: I II III IV V

(circle one)

Name of researcher completing the form: _____

Signature: _____ Date: ___/___/___

CASE REPORT FORM (CRF 3)

Please complete in block capitals and in black ink

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

CLINICAL FEATURES (pre-operatively)

	Leg		Buttock		Back		Dermatome /Myotome
	Yes	No	Yes	No	Yes	No	
Pain							
Duration (months)							
Paraesthesia							
Duration (months)							
Weakness							
Duration (months)							

COST EFFECTIVENESS OF LUMBAR LAMINECTOMY VS XSTOP

CASE REPORT FORM (CRF 4)

Please complete in block capitals and in black ink

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PREOPERATIVE IMAGING

CT Lumbar Date: __/__/__

MRI Lumbar Date: __/__/__

CT Mvelogram Date: __/__/__

X rays Date: __/__/__

Lumbar Spinal Stenosis confirmed **please tick**

L1/2	<input type="checkbox"/>
L3/4	<input type="checkbox"/>
	<input type="checkbox"/>
L4/5	<input type="checkbox"/>

CASE REPORT FORM (CRF 7)

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PATIENT ASSESSMENT: 6 weeks 6 months 12months 24 months

(circle one)

CLINICAL FEATURES (post-operatively)

	Leg		Buttock		Back		Dermatome /Myotome
	Yes	No	Yes	No	Yes	No	
*Pain							
Duration							
Paraesthesia							
Duration							
Weakness							
Duration							

* If you tick response Yes for Pain please include the VAS score.

Please complete in block capitals and in black ink

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PATIENT ASSESSMENT: Preop, Discharge (EQ5D, ZCQ Symptoms component) 6 weeks 6 months
12months 24 months

(circle one)

OUTCOME QUESTIONNAIRES

OUTCOME QUESTIONNAIRE SCORES & IMAGING

QBPDS(see CRF 7 -1) _____

EQ5D (see CRF 7 -2)

- Mobility __ Self-care__ Usual activities__ Pain/Discomfort__ Anxiety/Depression__

- Total score:

--	--	--	--	--

 - Health state: _____

ODI (see CRF 7-3)

_____ % (10 parts, each part score 0 – 5, final score(%) = total score/50 x 100%)

ZCQ Symptom Severity ____ **Physical Function** ____ **Satisfaction scale** ____

SF36 (see CRF 7- 5) PF__ RP__

BP__ **GH**__ **VT**__ **SF**__ **RE**__ **MH**__

CASE REPORT FORM (CRF 8-1)

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PATIENT ASSESSMENT: PREOP 6 weeks 6 months 12months 24 months

(circle one)

The Quebec Back Pain Disability Scale

This questionnaire is about the way your back pain is affecting your daily life. People with back problems may find it difficult to perform some of their daily activities. We would like to know if you find it difficult to perform any of the activities listed below, because of your back. For each activity there is a scale from 0 to 10

(0, not difficult at all; 5, moderately difficult; 10, extremely difficult).

Please choose one response option for each activity (please do not skip any activity) and circle the corresponding number.

Today, do you find it difficult to perform the following activities because of your back?

Get out of bed0 1 2 3 4 5 6 7 8 9 10

Sleep for at least 6 hours0 1 2 3 4 5 6 7 8 9 10

Turn over in bed0 1 2 3 4 5 6 7 8 9 10

Travel 1 hour in a car.....0 1 2 3 4 5 6 7 8 9 10

Stand up for 20-30 minutes.....0 1 2 3 4 5 6 7 8 9 10

Sit in a chair for several hours.....0 1 2 3 4 5 6 7 8 9 10

Climb one flight of stairs.....0 1 2 3 4 5 6 7 8 9 10

Walk a few blocks (300-400 m)..... 0 1 2 3 4 5 6 7 8 9 10

Walk several miles.....0 1 2 3 4 5 6 7 8 9 10

Reach up to high shelves.....0 1 2 3 4 5 6 7 8 9 10

Throw a ball.....0 1 2 3 4 5 6 7 8 9 10

Run two blocks.....0 1 2 3 4 5 6 7 8 9 10

Take food out of the refrigerator.....0 1 2 3 4 5 6 7 8 9 10

Make your bed.....0 1 2 3 4 5 6 7 8 9 10

Put on socks (pantyhose)..... 0 1 2 3 4 5 6 7 8 9 10

Bend over a sink for 10 minutes.....0 1 2 3 4 5 6 7 8 9 10

Move a table.....0 1 2 3 4 5 6 7 8 9 10

Pull or push heavy doors.....0 1 2 3 4 5 6 7 8 9 10

Carry two bags of groceries.....0 1 2 3 4 5 6 7 8 9 10

Lift 40 lbs (heavy suitcase)..... 0 1 2 3 4 5 6 7 8 9 10

Name of researcher completing the form: _____

Signature: _____

Date: ___/___/_____

Please complete in block capitals and in black ink

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PATIENT ASSESSMENT: Preop Discharge 6 wks 6 mths 12mths 24mths (circle one)

EQ5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual activities (e.g. work, study, housework, family or Leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing usual activities
- I am unable to perform my usual activities

Pain/Discomfort

I have no pain or discomfort

I have moderate pain or discomfort

I have extreme pain or discomfort

Anxiety/Depression

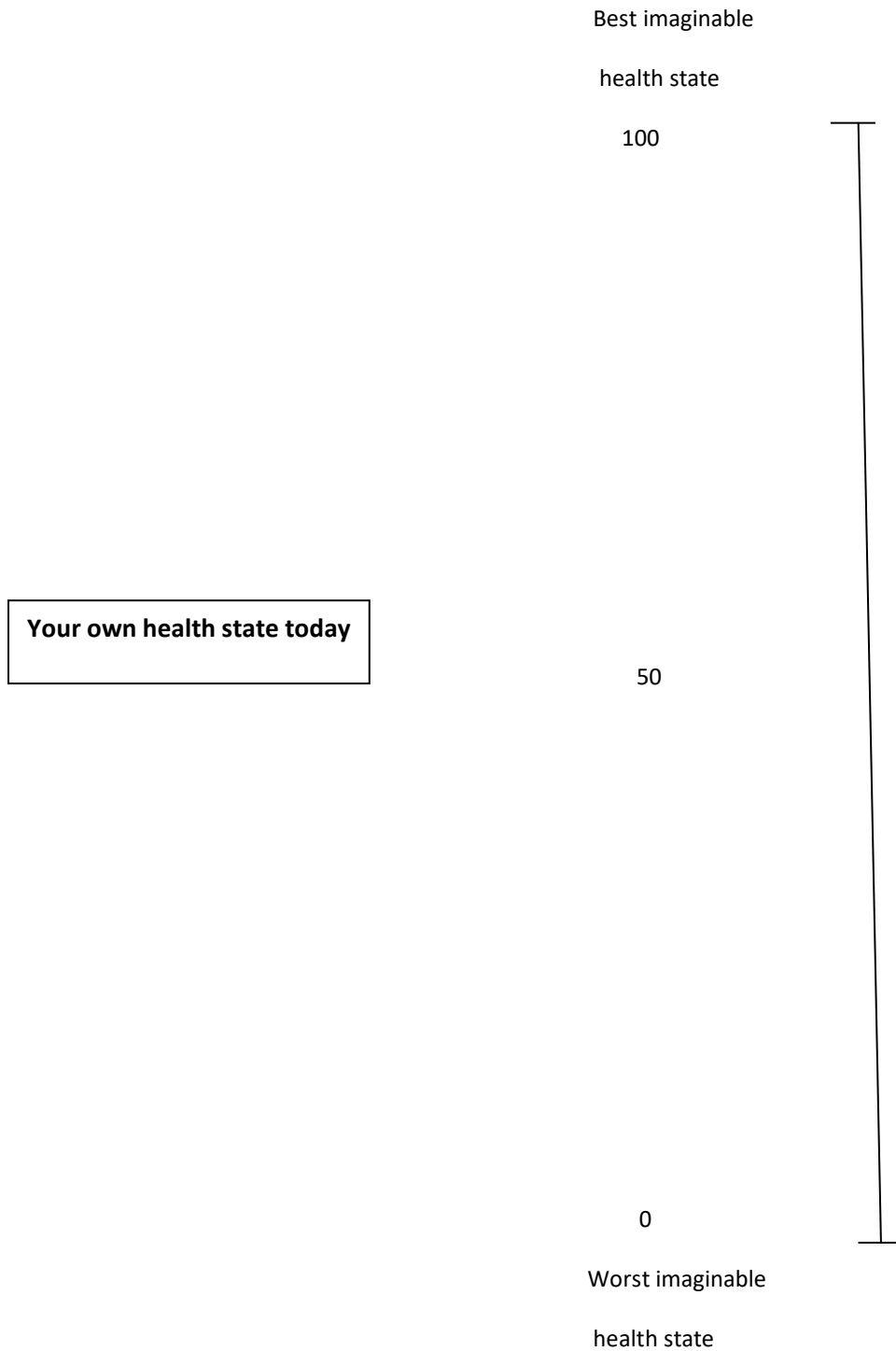
I am not anxious or depressed

I am moderately anxious or depressed

I am extremely anxious or depressed

EQ5D -CONTINUED

Best Imaginable Health State – We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



CASE REPORT FORM (CRF 8-3)

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PATIENT ASSESSMENT: PREOP 6 weeks 6 months 12months 24 months

(circle one)

OSWESTRY DISABILITY INDEX

Please Read: This questionnaire is designed to enable us to understand how much your low back has affected your ability to manage everyday activities. Please answer each Section by circling the ONE CHOICE that most applies to you. We realize that you may feel that more than one statement may relate to you, but please just circle the one choice which closely describes your problem right now.

SECTION 1—Pain Intensity

I can tolerate the pain I have without having to use painkillers

The pain is bad but I can manage without painkillers.

Painkillers give complete relief from pain

Painkillers give moderate relief from pain

Painkillers give very little relief from pain

Painkillers have no effect on the pain and I do not use them

SECTION 2—Personal Care

I can look after myself normally without causing extra pain.

I can look after myself normally but it causes extra pain.

It is painful to look after myself and I am slow and careful

I need some help but manage most of my personal care

I need help every day in most aspects of self-care.

I do not get dressed. I wash with difficulty and stay in bed

SECTION 3 –Lifting

I can lift heavy weights without extra pain

I can lift heavy weights but it gives extra pain

I can't lift heavy objects from off the floor but off the table is OK.

I can't lift heavy objects but light to medium ones are OK.

I can only lift very light weights

I cannot lift or carry anything at all.

SECTION 4 – Walking

Pain does not prevent me from walking any distance.

Pain prevents me from walking more than one mile.

Pain prevents me from walking more than one-half of mile.

Pain prevents me from walking more than one-quarter of mile.

I can only walk while using a cane or on crutches

I am in bed most of the time and have to crawl to the toilet.

SECTION 5 – Sitting

I can sit in any chair as long as I like without pain

I can only sit in my favourite chair as long as I like.

Pain prevents me from sitting more than one hour

Pain prevents me from sitting more than ½ hour

Pain prevents me from sitting more than ten minutes.

Pain prevents me from sitting at all.

SECTION 6 – Standing

I can stand as long as I want without extra pain.

I can stand as long as I want but it gives extra pain

Pain prevents me from standing for more than one hour

Pain prevents me from standing for more than 30 minutes

Pain prevents me from standing for more than 10 minutes

Pain prevents me from standing at all

SECTION 7 – Sleeping

Pain does not prevent me from sleeping well

I can sleep well only by using tablets

Even when I take tablets I have less than six hours of sleep

Even when I take tablets I have less than four hours of sleep

Even when I take tablets I have less than two hours of sleep

Pain prevents me from sleeping at all.

SECTION 8 – Sex Life

My sex life is normal and causes no extra pain.

My sex life is normal but causes some extra pain.

My sex life is nearly normal but is very painful.

My sex is severely restricted because of pain.

My sex life is nearly absent because of pain.

Pain prevents any sex life at all.

SECTION 9 – Social Life

My social life is normal and gives me no extra pain.

My social life is normal but increases the degree of pain

I can't participate in more energetic activities like dancing or tennis

Pain restricts my social life and I don't go out as often.

Pain restricts my social life at home.

I have no social life because of pain.

SECTION 10 – Travelling

I can travel anywhere without pain.

I can travel anywhere but it gives me extra pain.

Pain is bad but I manage journeys over two hours.

Pain restricts me to journeys of less than one hour.

Pain restricts me to short necessary journeys of less than 30 minutes.

Pain prevents me from travelling.

CASE REPORT FORM (CRF 8-4)

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PATIENT ASSESSMENT: PREOP 6 weeks 6
months 12months 24 months

(circle one)

ZURICH CLAUDICATION QUESTIONNAIRE

Please Read: This questionnaire has been designed to give the doctor information as to how your back pain has affected your ability to manage in everyday life. Please answer every section by circling the ONE CHOICE that most applies to you. We realize you may consider that two of the statements in any one section relate to you, but please just circle the one choice *which* most closely describes your problem.

Part 1: Symptom Severity Scale

In the last month, how would you describe:

Question 1. The pain you have had on average including the pain in you back, buttocks and pain that goes down your legs?

1. None
2. Mild
3. Moderate
4. Severe
5. Very severe

Question 2. How often have you had back, buttock, or leg pain?

1. Less than once a week
2. At least once a week
3. Everyday, for at least a few minutes
4. Everyday, for most of the day
5. Every minute of the day

Question 3. The pain in your back or buttocks?

1. None
2. Mild
3. Moderate
4. Severe
5. Very severe

Question 4. The pain in your legs or feet?

1. None
2. Mild
3. Moderate
4. Severe
5. Very severe

Question 5. Numbness or tingling in your legs or feet?

1. None
2. Mild
3. Moderate
4. Severe
5. Very severe

Question 6. Problems with your balance?

1. No, I have had no problems with balance
2. Yes, sometimes I feel my balance is off, or that I am not sure footed
3. Yes, often I feel my balance is off, or that I am not sure footed

PART 2 Physical Functioning Scale

In the last month on a typical day,

Question 7. How far have you been able to walk?

1. Over 2 miles
2. Over 2 blocks, but less than 2 miles
3. Over 50 feet, but less than 2 blocks
4. Less than 50 feet

Question 8. Have you taken walks outdoors or in the shopping centres?

1. Yes, comfortably
2. Yes, but sometimes with pain
3. Yes, but always with pain
4. No

Question 9. Have you walked around the different rooms in your house or apartment?

1. Yes, comfortably
2. Yes, but sometimes with pain
3. Yes, but always with pain
4. No

Question 10. Have you walked from your bedroom to the bathroom?

1. Yes, comfortably
2. Yes, but sometimes with pain
3. Yes, but always with pain
4. No

PART 3: Satisfaction Scale

How satisfied are you with?:

Question 11. The overall result of back operation

1. Very satisfied
2. Somewhat satisfied
3. Somewhat dissatisfied
4. Very dissatisfied
5. No operation

Question 12. Relief of pain following the operation?

1. Very satisfied
2. Somewhat satisfied
3. Somewhat dissatisfied
4. Very dissatisfied

Question 13. Your ability to walk following the operation

1. Very satisfied
2. Somewhat satisfied
3. Somewhat dissatisfied
4. Very dissatisfied

Question 14. Your ability to do housework, yard work, or job following the operation?

1. Very satisfied
2. Somewhat satisfied
3. Somewhat dissatisfied

4. Very dissatisfied

Question 15. Your strength in the thighs, legs and feet?

1. Very satisfied
2. Somewhat satisfied
3. Somewhat dissatisfied
4. Very dissatisfied

Question 16. Your balance or steadiness on your feet?

1. Very satisfied
2. Somewhat satisfied
3. Somewhat dissatisfied
4. Very dissatisfied

COST EFFECTIVENESS OF LUMBAR LAMINECTOMY VS XSTOP

CASE REPORT FORM (CRF 8-5)

Please complete in block capitals and in black ink

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

PATIENT ASSESSMENT: Preop 6 wks 6 mths 12mths 24 mths

(circle one)

STANDARD SF-36

INSTRUCTIONS: This survey asks your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

In general, would you say your health is: (circle one)

Excellent..... 1

Very good2

Good3

Fair.....4

Poor.....5

2. Compared to one year ago, how would you rate your health in general now

(circle one)

Much better now than one year ago1

Somewhat better now than one year ago.....2

About the same as one year ago.....3

Somewhat worse now than one year ago.....4

Much worse now than one year ago.....5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle a number on each line)

ACTIVITIES	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activity, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing several flights of stairs	1	2	3
Climbing one flight of stairs	1	2	3
Bending, kneeling, or stooping	1	2	3
Walking more than a mile	1	2	3
Walking half a mile	1	2	3
Walking 100 yards	1	2	3
Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one)

- Not at all.....1
- Slightly.....2
- Moderately.....3
- Quite a bit.....4
- Extremely.....5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

- None.....1
- Very mild.....2
- Mild.....3
- Moderate.....4
- Severe.....5
- Very severe.....6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

- Not at all.....1
- A little bit.....2
- Moderately.....3
- Quite a bit.....4
- Extremely.....5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks –

(circle one)

	All of the time	Most of the time	A good bit of time	Some of the time	A little of the time	None of the time
a. Did you feel full of life	1	2	3	4	5	6
b. Have you been a very nervous person	1	2	3	4	5	6
c. Have you felt so down that nothing could cheer you up	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy	1	2	3	4	5	6
f. Have you felt downhearted and low?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?

(circle one)

All of the time.....1

Most of the time.....2

Some of the time.....3

A little of the time.....4

None of the time.....5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get ill a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

COST EFFECTIVENESS OF LUMBAR LAMINECTOMY VS XSTOP

CASE REPORT FORM (CRF 8-6)

Please complete in block capitals and in black ink

CENTRE:

PATIENT HOSPITAL NUMBER.....

PATIENT ID.....

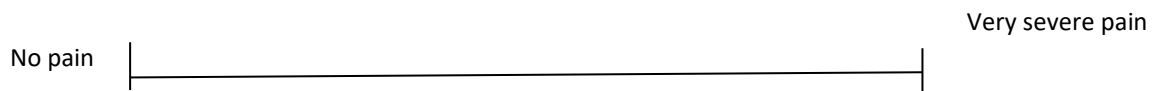
PATIENT ASSESSMENT: Preop Discharge 6 wks 6 mths 12mths 24 mths

(circle one)

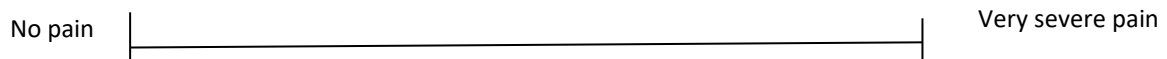
VISUAL ANALOGUE SCALE

How severe is your pain today? Place a vertical mark on the line below to indicate how bad you feel your pain is today.

BACK PAIN



LEG PAIN



Project ID: 08/H0711/12

1. Study title

Cost Effectiveness & Quality of Life after Treatment of Lumbar Spinal Stenosis with the XSTOP^{PK} IPD Device or Laminectomy: A Prospective Randomised trial

2. Invitation paragraph

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. What is the purpose of the study?

One of the main causes of lower back pain is due to age-related changes in the joints and ligaments of the back causing narrowing of the spinal canal where all the nerves travel, and compression of nerve roots. This condition is called Lumbar Spinal Stenosis (where “Lumbar” means lower back and “Stenosis” means narrowing). This results in a debilitating pain or heaviness in the legs that is aggravated by walking, thereby limiting mobility. Both the conventional operation of lumbar laminectomy and the use of the newer XSTOP-device have been shown to be effective methods for treatment. However, little is known regarding the costs and how patients function in everyday activities after they underwent one of these 2 procedures.

The purpose of this study is to document the total costs for the operative procedures, the degree of back-pain after the operations, the length of hospital stay and complication rate on short and long term basis, after having undergone either a lumbar laminectomy or the implantation of the XSTOP device. Also, the quality of life before and after the 2 procedures will be evaluated by completing specific questionnaires.

The data collected from your X-rays and the study forms completed by your surgeon’s staff will be analysed to determine if there is a significant difference between these two treatments.

The additional cost of the XSTOP device itself has to be weighed against any advantages to quality of life.

4. Why have I been chosen?

You are being invited to participate in this study because you suffer from Lumbar Spinal Stenosis at one or two levels in your back, and have tried to obtain symptomatic relief with previous non-surgical treatment methods, but without success.

5. Do I have to take part?

It is up to you to decide whether to take part. If you decide to take part you will be given this information sheet and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. You may choose to have one treatment rather than the other, but if this is the case, you will not be included in the study. If significant new findings develop during the course of the study that may affect your health or willingness to participate, you will be informed.

6. What is involved in the study?

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

If you agree to take part, you would be asked to follow all the instructions given to you by the doctors, nurses and other health personnel as per routine practice in that hospital. You would be asked to visit the hospital 6 times during the 2-year follow-up period.

At your initial visit, the doctor would review your medical history including the nature of your back pain to make sure that your participation meets the study requirements. If you agree, are eligible to participate and have signed the Informed Consent Form, your doctor will enrol you into the study. Randomisation envelopes will be opened by your doctor on the day prior to surgery. This means that you only then will be assigned to either the Laminectomy-treatment group or the XSTOP-device treatment group. Until those randomisation envelopes are opened, neither your doctor nor you will know to which group you will be assigned.

If you wish to withdraw from the study you have the right to do so at any time, in which case your treatment will not be affected in any way.

b. What will I be required to do?

b1. Pre-operative assessments:

The following information would be discussed and recorded for both treatment groups pre-operative:

Your initials, date of birth, weight and height

Your diagnosis and relevant medical history

Diagnostic measures including:

CT (=Computerised Tomography) scan of your spine: - the CT-machine takes a lot of picture of your spine from different angles. The CT scan of your spine will only be done during this study if you do not have previous CT images, CT images taken long time ago or the surgeon believes that the existing CT images are unsatisfactory and need repeating.

AND/OR:

MRI(=Magnetic Resonance Image) scan of your spine: - the MRI-machine produces high quality images of the spinal cord and the surrounding nerves, discs and ligaments.

CT Myelogram (this investigation will be performed only if unable to get an MRI of your spine because of any existing contraindications e.g. pacemaker). - this procedure is the same as for getting a CT of your spine (described above) with an additional procedure of receiving an injection of a small amount of liquid contrast through a small catheter placed in your spinal canal to enhance the picture.

All the above investigations and documentation is part of routine clinical practice, whether you are part of this study or not. The following questionnaires are for patients who agree to take part in this study:

Your doctor will go over the Inclusion and Exclusion criteria with you to see if you qualify to participate in this study.

You will be asked to rate your average back pain level over the past week on a scale of 0-10 (VAS).

You will be asked to complete the following 5 questionnaires about your activity level and quality of life:

- Quebec Back Pain Disability Scale(QBPDS) - -to assess your quality of life

EQ5D – to assess your general health and well being

SF36 - to assess your general health and well being

Oswestry Disability Index (ODI) – to assess pain disability due to Lumbar Spinal

Stenosis

Zurich Claudication Questionnaire (ZCQ) – to check pain and disability due to Lumbar

Spinal Stenosis

The total time to fill in all the questionnaires should be on average 10-20 minutes. If you would like, a member of the medical team will be available to read and explain the questionnaires to you.

b2. Treatment Procedure:

The following information would be reported at time of the operation as per routine clinical practice:

Assigned operation

Amount of blood loss

Duration of procedure

All procedures performed will be documented

Implant information (if assigned to the XSTOP-group) e.g. size of the implant used

Intra-operative complications, if any

b3. Follow-up assessments on the following visits: 7 days, 6 weeks, 6 months, 12 and 24 months:

The following information would be reported at the above mentioned time-points:

The length of your hospital stay

X-rays: will be performed as per hospital standard practice.

The following questionnaires (same as in Section 6(b1)) are for patients who agree to take part in this study:

You will be asked to rate your average back pain level over the past week on a scale of 0-10 on Visual Analogue Scale(VAS).

You will again be asked to complete the following 5 questionnaires about your activity level and quality of life:

EQ5D

QBPDS

SF 36

Oswestry Disability Index (ODI)

Zurich Claudication Questionnaire (ZCQ)

7. Which are the procedures that are being examined?

A. LUMBAR LAMINECTOMY Treatment group

Lumbar laminectomy is a relatively safe operation where some bone and soft tissues (ligaments) are removed to free up space in the spinal canal and foramina (the opening where the nerve roots exit the spine). This way the pressure on the spinal cord and nerve roots decreases and will result in symptom relief.

Procedure:

The patient lies in face-down position under general anaesthesia. An incision is made and the spine is dissected to the level where the decompression will be performed. Decompression of the spinal cord and nerve(s) will be done by removing some parts of the bone of the spine causing the compression. As a result the pressure on the nerve roots decreases which will result in relief of symptoms.

B. XSTOP Implant Treatment group:

The XSTOP is a metal implant (*Fig 1*) that fits between the two bony processes of the spine and away from the spinal cord and nerves.

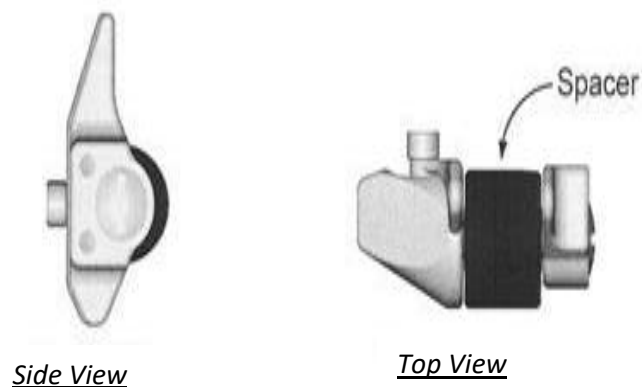


Fig 1: The image of the XSTOP

This is a minimally invasive surgical procedure, during which the device is generally implanted under local anaesthesia (with you awake) or general anaesthesia (with you asleep under general anaesthetic) and by a minimal open approach to your back at no more than 2 disc levels. The beneficial effect of the XSTOP implant is based on the fact that it will widen the spinal canal hence free up space for the compressed spinal cord and nerves to decompress.

Procedure:

The patient is positioned on the side, or face down. An incision is made and the XSTOP implant is placed in the created space between the bony processes of the spine. If applicable, a second XSTOP will be placed in a

similar manner at a neighbouring level. This way the spinal canal and the openings where the nerves exit the spine are widened. This pressure-reduction should result in pain relief.

8. What are known risks of the study or the side effects of any treatment received?

General Surgical Risk assessment:

There are two categories of risk factors to consider here, namely that associated with general spinal surgery and also that associated with any specific surgical procedures linked to the instrumentation (surgical tools used for performing the procedure) being used.

General risks include anaesthetic-related problems, circulatory problems, a collapsed lung, pneumonia, blood clots, intra-operative damage to blood vessels, soft tissue, or nerves or an allergic reaction to blood products or medications such as antibiotics and anaesthetic agents. In very rare instances, heart attack or death may occur.

Specific risks to XSTOP are very rare and include migration of the implant (1%), malpositioning of the implant (1%), migration of the implant (1%), fracture of a part of the bony process (1%), increased pain at implant level (1%).

Some specific risks to Lumbar Laminectomy again are rare and include the Spinal fluid leak, infection, recurrence of symptoms.

Although these complications are extremely rare, they may require additional surgery, extend the duration of surgery or extend the duration of the hospital stay. Damage to the spinal cord, usually limited to Spinal fluid leak, can occur rarely during surgery, especially where fine dissection of bone is required for decompression.

Pregnancy (relevant to female patient participants):

There is exposure to radiation from standard X-rays taken to diagnose and follow-up your spinal stenosis and the status after surgery. There is also radiation exposure during surgery from the CT-scan described above. The radiation from X-rays and the CT-scan used during the surgery may be harmful to an unborn child.

Women who could become pregnant must use an effective contraceptive during the course of this study. Thus, if you are a woman who could become pregnant, you must have a pregnancy test done prior to your enrolment into the study. If your test is positive, these study tests will be cancelled, and you will not be eligible for enrolment into this study. Also, breastfeeding will exclude you from participation. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her doctor.

Risk study-participation:

Participation in the study per se, does not introduce any additional risk for you, because the study will follow normal routine practice used in your hospital for both procedures, in term of surgical technique, radiographic review and follow-up visits. Most hospitals already collect some form of outcome data, so the only additional inconvenience for you will be the need to complete 5 questionnaires instead of one.

9. What are the possible benefits of taking part?

General Surgical Benefit assessment:

Both operations have been shown to be effective in the treatment of lumbar spinal stenosis. The degree of benefit expected will be discussed with you by your surgeon, since this depends on other factors also.

The benefits of spinal surgery include the potential to dramatically improve a patient's quality of life by enabling them to become more active and take a more constructive part in society. This is achieved by the removal of the cause of their pain and through rehabilitation reduces their dependence on the medical system for long term medical treatment. The level of improvement is linked to the other pre-existing medical conditions.

Benefit study-participation:

The only benefit for you from participation in the study is linked to the data collection and regular review, which could identify any potential problems earlier. You will also have an additional point of contact with regard to your condition. That contact would be the research fellow who is a neurosurgeon in training especially employed for this study who will be contactable at any time (this depends on the site involved).

10. Payment for participation

You will not be paid for participation in this study.

11. Costs for participation

No costs for study participation will be passed on to you.

12. Confidentiality

Your privacy and all personal health information will remain confidential and will not be released without your written permission to the extent permitted by law. You are giving permission to your doctor to enter data regarding your treatment and physical status into a database. The information gathered will not include your name. Your data will be identified by an assigned identification number and your initials. The anonymous database information may be analysed to identify trends that may be used in scientific publications or presentations. Any publication of data will not identify you in any way.

The custodian of the data will be UCLH Foundation Trust, will be responsible for the security of the data. The data will not be stored for longer than 10 years.

By signing this consent form, you give permission for the release of the information gathered from your participation in the study to the funding Company (Kyphon), for possible publication by Mr. Choi and / or other

doctors participating in this study. Your medical records may also be reviewed by representatives of the funding company (Kyphon), by the Institutional Review Board / Ethics Committee and by representatives of the FDA or other regulatory representatives for the purpose of verifying medical information relating to this study. In addition, your doctors and other study staff at the hospital may review your medical records to collect the appropriate data for the study. The data collected in this study may be submitted to the FDA, published in medical journals, and/or presented at physician meetings. The privacy and confidentiality of your individual records will be strictly maintained as per Data Protection Act.

Data may be transmitted outside the European Union.

Your general practitioner will be informed if you decide to take part in the study. We will not inform your GP if you do not want us to do so.

13. What happens if something goes wrong?

In case you have any concern or complaint about any aspect of this clinical trial, you should ask to speak with the project's Chief Investigator, who will do his best to answer your questions.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you. Details are to be obtained from the hospital.

14. Who is organising and funding the research?

This is a multicentre, non-commercial study which will run at the National Hospital for Neurology and Neurosurgery (London), St Georges Hospital (London) and Brighton and Sussex County hospitals.

15. Withdrawal from the project

Your participation in the trial is entirely voluntary. You are free to decline, to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the trial, or to withdraw once entered, this will in no way affect your future medical care.

All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Your medical records may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

16. Who has reviewed the study?

The study was reviewed and approved by the Internal Review Panel at the National Hospital for Neurology and Neurosurgery, London as well as the Charing Cross Research Ethics Committee.

17. Contacts for further information

If you have any further questions about the study, *the investigators within your hospital* would be delighted to answer them for you.

The investigators for various sites are: (This information was removed from this thesis as per UCL's guidelines)

If you wish to seek independent advice or assistance you may contact the Patient Advice and Liason Service (PALS) at the hospital where you were treated.

Centre Number:

Patient Identification Number for this trial:

CONSENT FORM

Cost Effectiveness & Quality of Life after Treatment of Lumbar Spinal Stenosis with the XSTOP^{PK} IPD Device or Laminectomy: A Prospective Randomised trial

(Protocol Number – 07/X01)

Name of the Investigator:

Please initial box

1. I confirm that I have read and understand the patient information sheet dated 05/03/2008
(version 1.3) for the above study and have had the opportunity to ask questions.

2. I confirm that I had sufficient time to consider whether I want to be included in the study.

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

4. I understand that sections of any of my medical notes may be looked at by responsible individuals from UCLH, Kyphon Europe or from regulatory authorities where it is relevant to my taking part in research.
I give permission for these individuals to have access to my records.

5. I agree to take part in the above study.....

Name of Patient Date Signature

Name of Person taking consent Date Signature

(if different from researcher)

Researcher

Date

Signature

(to be contacted if there are any problems)

Comments or concerns during the study:

If you have any comments or concerns you may discuss these with the Investigator / Researcher. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL Hospitals. Please quote the UCLH project number at the top this consent form.

When completed, 1 form for the patient; 1 to be kept as part of the study documentation for the trial master/investigator site file; 1 original to be kept with the hospital medical notes.

CONFIDENTIAL

GP Information Sheet

Version 1.0

Cost Effectiveness & Quality of Life after Treatment of Lumbar Spinal Stenosis with the XSTOP^{PK} IPD Device or Surgical Decompression: A Prospective Randomised trial

(Protocol Number – 07/X01)

Dear Dr,

Background to the study

Lumbar spinal stenosis (LSS) is a common and debilitating condition which consumes large amounts of healthcare resource. It occurs in 13-14% of patients who consult a specialist with back-pain, and is a considerable drain on NHS resources.

Degenerative changes in the facet joints and ligamentum flavum cause narrowing of the spinal canal and compression of nerve roots. This results in a debilitating pain or heaviness in the legs that is aggravated by walking, thereby limiting mobility. There have been an increasing number of treatments for LSS over the years, including physiotherapy, conventional surgery (eg. lumbar laminectomy) and implantation of devices called interspinous distractors. Lumbar laminectomy and interspinous distraction are both effective methods for treatment of LSS but there is little known about the relative cost effectiveness of these treatments and quality of life for patients after treatment.

Both the conventional operation of lumbar laminectomy and the newer XSTOP device are relatively safe operations and have both been shown to be effective treatments. However, we need to establish whether there is a difference in the operative times, degree of back-pain after the operations, length of hospital stay, or complication rate between the procedures. The additional cost of the XSTOP device itself has to be weighed against any advantages to quality of life. This constitutes the basis for this study, which is sponsored by St Francis Medical Technologies Inc/ Kyphon.

What will be involved?

Your patient has symptomatic LSS and has agreed to take part in the study. They will be randomly allocated to have either the conventional lumbar laminectomy (and equivalent surgeries), or the insertion of the XSTOP device.

Aftercare and follow-up arrangements will be the same, regardless of the treatment they receive. They will be reviewed in the out-patient clinic for 2 years following surgery.

What are the benefits to taking part?

Both operations have been shown to be effective in the treatment of lumbar spinal stenosis. The degree of benefit expected will be discussed individually, since this also depends on individual symptoms and patient factors.

Further questions?

If you have any further questions about the study, we would be delighted to answer them for you. Please contact. (Information withheld as per UCL's guidelines)