NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation supporting documentation

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) alongside the assessment report and assessment report overview.

Documents included are:

1. Adoption scoping report – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.

2. Sponsor submission of evidence – the evidence submitted to NICE by the notifying company.

3. Expert questionnaires – expert commentary gathered by the NICE team on the technology.

4. EAC correspondence log – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.

5. EAC supplementary report – Following a request from MTAC, the EAC agreed to investigate the impact of an extended timeline on health economic model submitted by SI-Bone for iFUSE.

Please use the bookmarks included in this PDF file to navigate to each of the above documents.

Medicines and Technologies Programme
Adoption Scoping Report MTG iFuse implant system for chronic sacroiliac joint pain

SUMMARY – for MTAC1 meeting

Adoption Levers

- Improvement in patient outcomes – an improvement in reported pain using the visual analogue scale of at least 50%
- Reduced length of stay following procedure –average length of stay is 1-2 days
- Reduced risk to patient compared with open surgery
- Easier clinical procedure leading to increased clinical confidence

Adoption Barriers

- Correct patient selection is essential
- Specialist table and x-ray equipment required to achieve correct implant position
- Training requirements vary depending on experience and specialism, currently this is not tailored
- Cost of technology

1. Introduction

The Adoption team has collated information from 2 healthcare professionals working within NHS organisations both of whom have experience of using the iFuse implant system. The team also reviewed the specialist advisor questionnaires submitted during the development of the NICE interventional procedures guidance (IPG) – Minimally invasive sacroiliac joint fusion surgery for chronic sacroiliac pain (published April 2017).

This adoption scoping report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt the technology into routine NHS use.

The iFuse implant system is intended for use in patients with chronic sacroiliac joint pain (SIJ). It consists of a sterile cannulated triangular titanium implant with porous surface and surgical instruments for implant.

It is implanted during a minimally invasive procedure under general or spinal anaesthesia, involving a small incision made over the lateral buttock to allow entry to the lateral access of the ilium. The implants are then placed across the sacroiliac joint uniting the ilium to the sacrum, and remain in place permanently. The procedure involves the insertion of a guide pin into the sacroiliac joint, guided by fluoroscopy. This guides a drill and a broach which creates a hole for the implant which is inserted over the guide pin into the joint. Ideally 3 implants are used where possible, depending on the size of the patient. If the patient's anatomical presentation doesn't enable this, the surgeon might then use just 2 implants.

2. Contributing organisations

The Adoption team spoke to 2 NHS clinicians, one consultant spinal surgeon and one consultant trauma and orthopaedic surgeon, both with direct experience of using this technology for patients with chronic sacroiliac joint (SIJ) pain.

The manufacturer has advised that there are 20 NHS organisations in the UK where at least one procedure with the iFuse implant system has been done.

3. Use of iFuse implant system in practice

One contributor, a pelvic trauma surgeon from an acute teaching hospital has been using the technology for 1 year and to date has done 16 surgeries with it. Other colleagues in the same trust, a spinal surgeon and another pelvic trauma surgeon, have done 4 and 2 respectively.

The other contributor, a consultant spinal surgeon from a tertiary centre, has been using the technology for 3 years and does approximately 10 surgeries each year.

Both contributors were positive about the overall effectiveness of the technology in practice but were reticent about the technology being used by all the clinical groups notified by the manufacturer (orthopaedic trauma surgeons, orthopaedic spinal surgeons, general orthopaedic surgeons and spinal neurosurgeons). One advised that additional training would be required for spinal surgeons and the other stated that they would be unsure about general surgeons using it as they do not regularly do this or similar surgery.

Both contributors stated that intraoperative x-ray was essential to use the technology and a theatre table of sufficient size and functionality is needed to allow for this. Contributors advised a specialised theatre imaging table with carbon fibre frame similar to the Jackson table would be required or an extended x-ray end for a normal theatre table is necessary. They reported that many hospitals may not have access to this specialist equipment which is reported to be costly.

One contributor reported using 3D navigation with this technology due to the risk of irreversible injury to the L5, S1 and other sacral roots during the preparation or the procedure. This contributor recommends that any clinician using this technology and doing this procedure should use 3D navigation but is only aware of one other centre in the UK where this is available.

The other contributor advised that in the absence of 3D navigation, the minimum expectation of a 2D x-ray is that it should be capable of doing digital subtraction images, should have a large enough distance between the emitter and receiver to get the inlet and outlet views and it should be of high enough resolution to see the sacral foramina.

They both advised that this level of imaging is required to ensure correct positioning of the implant.

4. Reported benefits

The benefits of adopting the iFuse implant system for chronic sacroiliac joint pain, as reported to the Adoption team by the healthcare professionals using the technology are:

- Reduced length of stay – some patients have been discharged on the same day, and the average is 1-2 days post-surgery. One contributor reported that when using a different technology for minimally invasive surgery the average length of stay was 2-4 days.
- The porous roughened surface allows for bone growth around and within the device increasing the stability of the implant.
- Easier to use than other technologies for minimally invasive sacroiliac joint fusions.

- Easier technique than open surgery for sacroiliac joint fusion.
- Less associated risks than open surgery for sacroiliac joint fusion.

5. Levers and barriers to adoption

The key considerations for adoption highlighted through discussions with expert contributors are:

Patient Selection

The effectives of this technology is dependent on the right patient selection which was cited as critical by both contributors and the specialist advisor commentators for the NICE Interventional procedures guidance. Diagnosing the source of pain to be the SIJ is done based on clinical history, sacroiliac joint stress clinical tests and a positive response to diagnostic injection under fluoroscopy. Contributors advised the latter is an absolute prerequisite to proceeding with minimally invasive surgery with the iFuse implant system.

Care pathway

The contributors advised that people are often referred postpartum or post trauma, or following spinal fusion or failed sacroiliac joint fusion. There is also a large group of patients who develop sacroiliac joint pain with no preceding factors. It is more common in women than in men. It is a common cause of back pain with up to 30% of low back pain coming from sacroiliac joints

Some people referred for this surgery require a wheelchair to mobilise due to severity of pain experienced.

The care pathway for this group of patients is provided in a stepped manner. Prior to referral for surgery a minimum of 6 months conservative management with rehabilitation from either a physiotherapist or a chiropractor and often input from the pain management service is required.

Some people will also have had radiofrequency denervation, and pain relief following this is reported to be 8-18 months. The contributors advised that this step is not always applicable, some patients may be undergoing a radiofrequency denervation procedure every 12 months.

Only very complex patients who have had an MRI scan within the previous three months and referred by a specialist will be accepted for review in the tertiary centre.

In the instance of bilateral chronic SIJ pain presentation, bilateral surgery is not done simultaneously. An interval of at least 6 months is suggested by the contributor.

Following surgery the patient is partial weight bearing for 4 weeks progressing to full weight bearing at 6 weeks. One contributor reported at the 3 month follow up appointment most patients are discharged, the other advised they follow up at 2 years to observe long term patient outcomes. Contributors report no requirement for therapeutic steroid injections post-surgery.

Clinician confidence / acceptance

Both contributors stated that this technology has increased their confidence in the surgical management of chronic SI joint pain, as the risk is reduced compared with open surgery.

It was highlighted that success relies on the experience and skill of the clinician in its use, ensuring it is positioned in the correct place.

Resource Impact

One contributor reported the cost of just the three implants to be almost £3,000.

Capacity

The contributor from the tertiary centre advised that he is the only clinician in his organisation doing this intervention and that they are compliant with the 18 week wait target.

The other clinician advised that in his organisation there can be a 40 week wait due to patients choosing to wait to see him, and the lack of appropriate theatre spaces with suitable tables. In order to meet targets the trust will refer some patients to a private hospital (with suitable tables) where the clinician also works.

Training

Appropriate training was cited by both contributors as vital.

One of the specialist advisors to the IPG advised that results of the procedure are dependent on the right patient selection, thorough work up to ensure the source of pain is the SIJ, good understanding of the regional anatomy and ability to interpret the intraoperative fluoroscopic images.

Both contributors advised that training should be tailored depending on experience and may need to include training on sacroiliac joint fusion prior to training on the technology.

One contributor attended a 2 day course provided by the manufacture which involved practical experience of using the technology on cadavers.

Both contributors agreed that there should be a mentoring and shadowing aspect to the training with individual trainers and trainees agreeing sign off on competency.

Patient experience

The contributors report that when the primary source of the pain is SIJ, using the iFuse implant system has always led to an improvement in reported pain, using the visual analogue scale, of at least 50%. They also report improvement in the other outcome measures used, EQ5D and Oswestry disability index (ODI).

Patient / Clinician safety

Neither contributor reported any issues with loosening or infection.

One contributor said they have encountered instances where the procedure has been stopped as they had been unable to obtain a clear x-ray view due to bowel gas or faecal impact, or if anatomically they have been unable to position the implant.

In the instance of bowel gas or faecal impact preventing clear x-ray views they will attempt the procedure at a later date.

Other

One contributor advised, despite being very experienced, they always have the manufacture representative present during the procedure, and would recommend this for any clinician, in particular during their first few procedures. This is to gain an expert opinion on the position of the implant.

6. Comparators

Neither contributor offers open surgery SIJ fusion, the specialist advisors to the IPG advised that this practice ceased being routine about 10 years ago.

Neither contributor identified a comparator for the iFuse implant system, although one reported previously using hollow cages.

If minimally invasive surgery with iFuse implant system is not done, conservative management using non-invasive treatments and analgesic medications is likely.

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Medical Technologies Evaluation Programme

Sponsor submission of evidence:

Evaluation title: MT355 iFuse Implant System

Sponsor: SI-BONE

Date sections A and B submitted:

Date section C submitted:

August 2011 (Version 1.1)

Contents

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]'). Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

Glossary of terms

Term	Definition
CM	Conservative Management
DS	Degenerative Sacroiliitis
ICER	Incremental cost-effectiveness ratio
iMIA	iFuse Implant System Minimally Invasive Arthrodesis (clinical trial sponsored by SI-BONE)
INSITE	Investigation of Sacroiliac Fusion Treatment (clinical trial sponsored by SI-BONE)
ITT	Intent-to-treat
LBP	Lower Back Pain (or Low Back Pain)
LOIS	Long-Term Follow-Up in INSITE/SIFI (clinical trial sponsored by SI-BONE)
LOTUS	Long Term Follow Up of Patients Implanted with the iFuse Implant System (clinical trial sponsored by SI-BONE)
MCID	Minimum Clinical Important Difference
MDR	Medical Device Reporting
MIS	Minimally Invasive Surgery
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSM	Non-Surgical Management
PT	Physical Therapy
QALY	Quality-adjusted life year
RF	Radiofrequency Ablation (also known as RFA)
SALLY	Study of bone growth in the Sacroiliac Joint after minimally invasive surgery with titanium implants (clinical trial sponsored by SI-BONE)
SD	Sacroiliac Dysfunction
SI	Sacroiliac
SIJF	Sacroiliac Joint Fusion
SIFI	Sacroiliac Joint Fusion with iFuse Implant System (clinical trial sponsored by SI-BONE)

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People with unresolved sacroiliac joint dysfunction		
Intervention	iFuse Implant System	Sacroiliac joint fusion using the iFuse Implant System	
Comparator(s)	• Open sacroiliac joint fusion surgery using screw or cage systems • Non-surgical or conservative management, including: o optimisation of medical therapy, o individualised psychological and physical therapy with provision of adequate information and reassurance o steroid injections • Sacroiliac joint denervation	Under Non-surgical or conservative management, ADD – Radiofrequency ablation (RFA) of the lateral branches of sacral nerve roots.	RFA was part NSM in the INSITE randomized controlled trial.
Outcomes	The outcome measures to consider include: **Patient outcomes** • back/ sacroiliac joint pain relief (including medicine use and post-operative pain scores); • improvement in function and disability from back pain (measured using Oswestry disability index (ODI) or other valid disability scale); • blood loss during surgery; • patient satisfaction; • patient health-related quality of life; • radiographic evidence of union and absence of loosening (x-ray or CT scan to measure bone growth across the fused joint); • time to return to work/normal activities; • peri-operative morbidity and device-related adverse events; • postoperative infection or complications; • reoperation rates. **System outcomes** • procedure time and resources • length of hospital stay.	Under Patient Outcomes, ADD – medication (opioid) use	In both INSITE and iMIA patients were asked at follow-up visits to indicate whether they were taking medication (opioids).

	Scope issued by NICE	Variation from scope	Rationale for variation
Cost analysis	**Comparator(s)**: Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.		
Subgroups to be considered	• women of reproductive age • number of implants inserted • unilateral versus bilateral sacroiliac joint implants • previous lumbar surgery	ADD “spine” I the bullet: • Previous lumbar spine surgery	Clarification to distinguish from other possible lumbar surgery.

	Scope issued by NICE	Variation from scope	Rationale for variation
Special considerations, including issues related to equality	People with chronic sacroiliac pain or lower back pain lasting more than one year may be considered disabled under the Equality Act 2010, if the condition has a substantial and long-term negative effect on their ability to do normal daily activities. Women may experience SIJ dysfunction due to the mechanism of childbirth. The sacroiliac joint and its free movement is critical to normal, vaginal delivery in childbirth. Women of reproductive age having SIJ implants would require caesarean section deliveries after iFuse implant insertion. Most people having surgical interventions for SIJ pain are female but over usual reproductive age. **Questions/Answers**: Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics? [YES] Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality? [NO] Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance? [NO]	Women of reproductive age having iFuse Implants on a single side (unilateral) may or may not be able to have a successful vaginal delivery. The presence of iFuse Implants should be disclosed to a pregnant woman's obstetrical care provider early in pregnancy and a collaborative decision should be made regarding delivery options and the possible need for a Caesarean section. If the woman has implants on both sides (bilateral) then a Caesarean section should be planned.	The company has anecdotal evidence that some patients who have undergone a unilateral MIS SI joint fusion with placement of iFuse Implants may be able to undergo uncomplicated vaginal delivery. One of the patients in the INSITE study and several other iFuse patients having successful vaginal delivery have been reported. Caesarean section is not without risk, and a woman should be allowed to participate in the decision making as to whether an attempt at vaginal birth should be made or not. Risks should be discussed, and a collaborative decision should be made regarding childbirth.

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

iFuse Implant System®

iFuse Implant (Diameters: 4.0, 7.0, 7.5, and 10.75mm; Lengths: 30-90mm)

iFuse-3D (Diameter: 4.0 and 7.0mm; Lengths: 30-90mm)

2.2 What is the principal mechanism of action of the technology?

Principles of Operation: Triangular shape minimizes rotation and stabilizes the joint after insertions through interference fit across the sacroiliac (SI) joint. Porous surface allows fixation/stabilization, fusion and bony ingrowth.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Sacroiliac (SI) Joint Dysfunction

The sacroiliac (SI) joint is part of the pelvic ring, linking the ilium bones of the lateral pelvis to the sacrum (lowest part of the spine). The primary role of the SI joint is to provide stability for the pelvis and to bear the load of the upper body. The SI joint is the largest joint in the human body, one of 8 major joints, and has a dual structure, with the upper part of the joint being ligamentous and the lower part being a true synovial joint. It is a diarthrodial joint (meaning that it has hyaline articular cartilage on both sides of the joint) similar to most all other joints. Multiple studies have shown the SI joint moves with normal daily activities [Sturesson 1989, 2000a, 2000b[1–3]; Kibsgård 2012, 2014[4,5]] and is subject to the same internal and external forces experienced by other joints throughout the body. As such, the SI joint may be damaged from acute or repetitive trauma. The SI joint is subject to the same pathologic processes that affect other joints in the body and hence is reasonably believed to be a potential pain source. The ligaments and soft tissues supporting the SI joint may be stretched or damaged leading to abnormal force/load transfer. The joint may be damaged by autoimmune, inflammatory, and/or infectious processes. The SI joint is also subject to degeneration secondary to underlying osteoarthritis or increased stress at the SI joint (*i.e.*, adjacent segment disorder) after lumbar fusion [Katz 2003[6], Maigne 2005[7], Ha 2008[8], Ivanov 2009[9]].

The SI joint is a proven “pain generator” or source of pain. The SI joint is highly innervated, and studies demonstrate an anatomic “pain pathway” from the SI joint to the brain [Ikeda 1991[10]; Fortin 1999, 2003[11,12]; Vilensky 2002[13]; Sakamoto 2001[14]; Szadek 2008, 2010[15,16]]. In normal volunteers, the SI joint responds to noxious stimuli, both mechanical and chemical [Fortin 1994a[17]], with production of SI joint pain in a typical pain referral pattern. Local anaesthetic injection into the joint eliminates SI joint pain induced by noxious stimuli. The complex innervation of the SI joint has been confirmed clinically by multisite anaesthetic injections in normal volunteers [Dreyfuss 2009[18]]. The totality of evidence strongly confirms that the SI joint meets the definition of a pain generator as it:

1) demonstrates innervation and an anatomic pain pathway, 2) reproduces typical pain in response to noxious stimuli, 3) local anaesthetic injection eliminates the pain, 4) the SI joint is subject to internal/external forces that

could damage the joint, and 5) definitive treatment (*e.g.*, with SI joint fusion) results in long lasting pain relief.

Multiple studies have evaluated the prevalence of the SI joint as a pain generator in patients presenting with lower back pain (LBP). Depending upon study methodology, the prevalence of the SI joint as a source of patients' LBP ranges from 15% to 30% [Bernard 1987[19], Schwarzer 1995[20], Maigne 1996[21], Irwin 2007[22], Sembrano 2009[23]]. In patients with continued or new onset LBP after lumbar fusion, the prevalence of the SI joint as the source of pain is even higher, ranging from 32% to 43% [Katz 2003[6], Maigne 2005[7], DePalma 2011[24], Liliang 2011[25]].

Symptoms of SI joint pain include off-center back pain below L5 and pain in the buttocks near the posterior superior iliac spine, with occasional radiation into the leg. Activities that typically worsen SI joint pain are prolonged sitting on the affected side, climbing or descending stairs and pain while driving over road bumps.

Causes of SI joint pain include trauma, such as motor vehicle accident, fall on buttocks, lifting and twisting, or childbirth. Degenerative processes are a common cause of SI joint dysfunction, resulting from increased stresses on the joints due to previous lumbar fusion, conditions such as osteoarthritis, repetitive movements, or lingering chronic pain after giving birth known as post-partum pelvic girdle pain (PPGP). About 50% of women have pelvic girdle pain during pregnancy and 25% experience pain after pregnancy [Wu 2004[26]]. Approximately 5% of all pregnant women continue to have PPGP 3 years following delivery [Norén 2002[27]]. A substantial proportion of PPGP is SI joint dysfunction.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

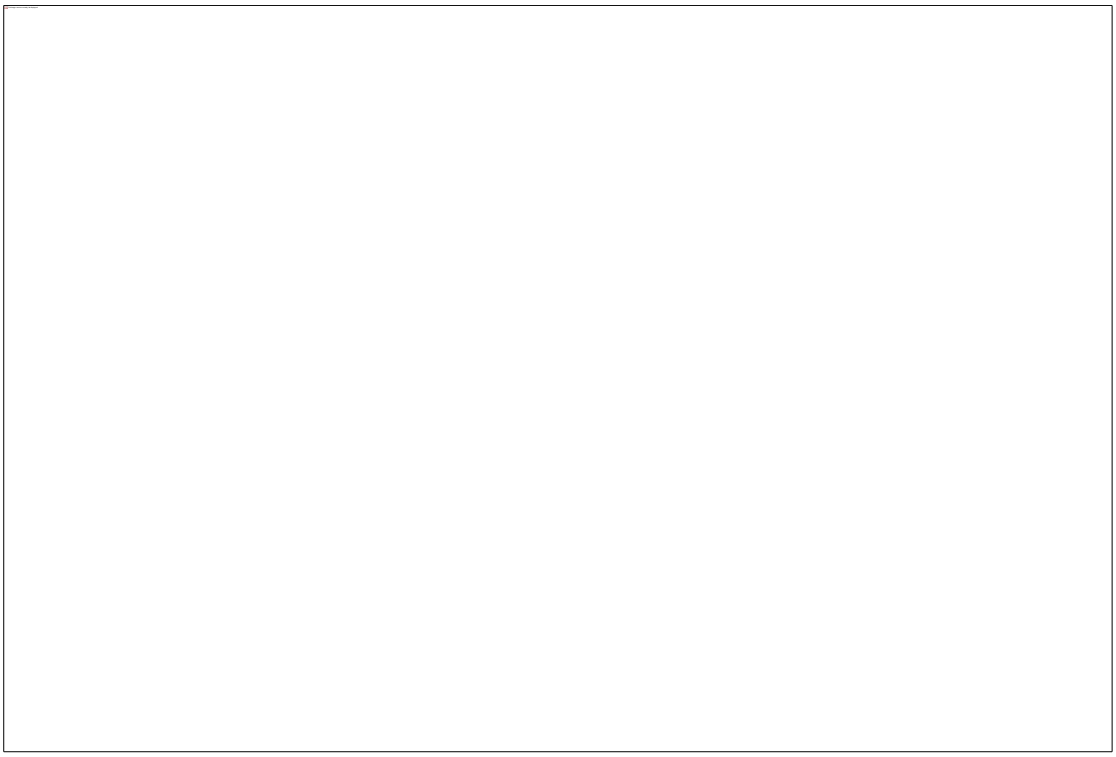
NICE Clinical Guideline – Low back pain and sciatica in over 16s: assessment and management

NICE Interventional Procedure Guidance [IPG578] Published date: April 2017 – Minimally invasive sacroiliac joint fusion surgery for chronic sacroiliac pain

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

The current clinical pathway of care for patients with chronic SI joint dysfunction typically consists of non-surgical treatment provided in a stepped manner from less invasive/costly to more invasive/costly. Treatment typically begins with medications (nonsteroidal anti-inflammatory drugs and/or opioids) and physiotherapy focused specifically on the SI joint. There is no high level clinical literature that supports the effectiveness of medications for treating non-autoimmune SIJ dysfunction. There is no high-level clinical evidence to support the effectiveness of physiotherapy for treatment of chronic SIJ dysfunction. For patients who do not respond to these first line measures, additional more invasive and more costly procedures are prescribed. The next step in the clinical pathway is typically SI joint intra-articular steroid injections. There is no high-level clinical evidence demonstrating that intraarticular SIJ steroid injections provide lasting improvement in pain or function. The next step in the clinical pathway is SI joint radiofrequency ablation (RFA). There is some clinical evidence that RFA does provide temporary (6-9 months or less) improvement in SIJ pain and an improvement in function of like duration. The next step in the clinical care pathway is minimally invasive (MIS) SI joint fusion performed via a lateral trans-articular approach utilizing the iFuse Implant System. The iFuse Implant™ has been shown in multiple studies to provide improvement in SIJ pain, function and quality of life. There is significant clinical evidence that MIS SI joint fusion performed with the iFuse Implant System is safe, effective, durable, and economically beneficial. Open SI joint fusion, in which the joint is accessed directly through standard surgical means, is more invasive/costly and may also be considered a treatment option after failed non-surgical management. There is no high level clinical evidence to support the safety or effectiveness of open SIJ fusion.

Figure 1 – Current Treatment Pathway



3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

The clinical care pathway, described above, is consistent with the NICE Interventional Procedures Guidance "Minimally invasive sacroiliac joint fusion surgery for chronic sacroiliac pain."

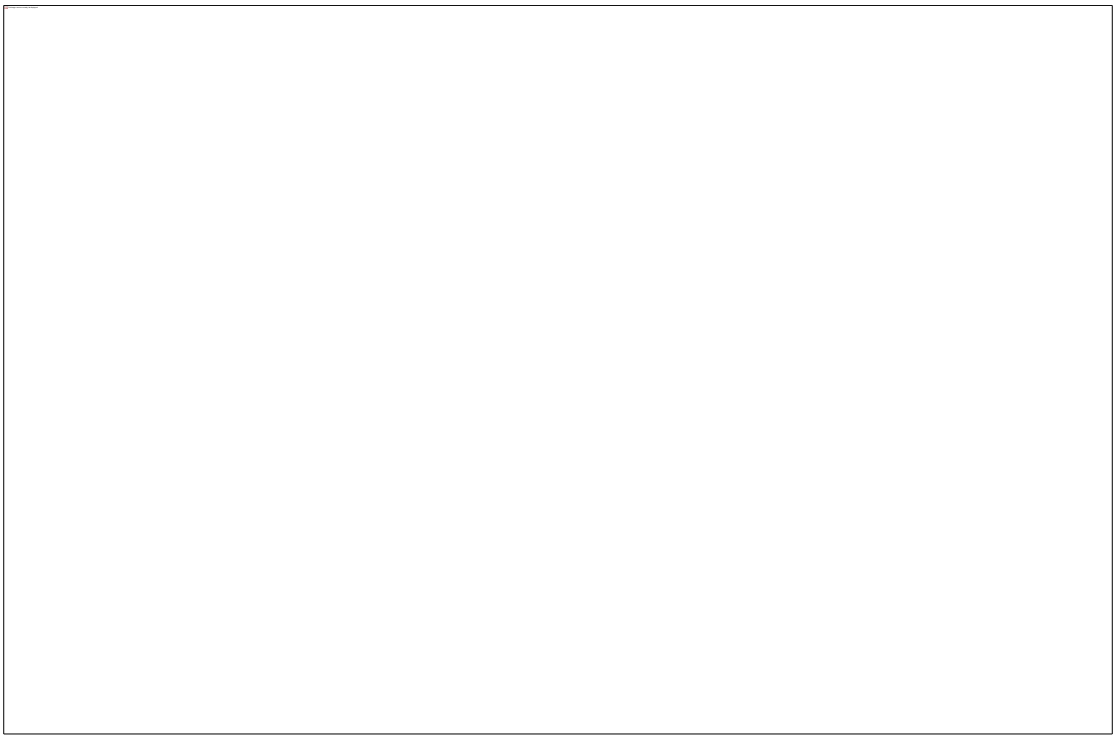
One issue related to the current clinical practice is a general "lack of awareness" of the condition (SI joint dysfunction). The condition is commonly diagnosed and treated by allied health practitioners such as physiotherapists, chiropractors and osteopaths. Physicians and surgeons are less aware of the condition, the accepted diagnostic algorithm and the clinical pathway for care. There has been a significant increase in awareness and knowledge of this condition in the last five years. However, there is still work to be done.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

If the iFuse technology is adopted by the NHS in England, there will likely be an increased awareness of the condition (SI dysfunction) and an increased knowledge, amongst health care practitioners, of the clinical care pathway for patients with this condition. As such, it is anticipated that a greater percentage of patients with chronic disabling low back pain will be appropriately evaluated for and ultimately diagnosed with SI joint dysfunction. Moreover, an increased likelihood of proper diagnosis may reduce the provision of inappropriate or misdirected surgery, which confers risk but no benefit and can be very expensive.

It is anticipated that the steps in the non-surgical care pathway will not change (medications, physiotherapy, steroid injections and possibly radiofrequency ablation). However, it is anticipated that fewer patients on this care pathway will continue to receive multiple rounds of repetitive non-surgical treatments that are not effective. It is anticipated that the appropriate patients will move through the non-surgical care pathway and will be offered the definitive treatment with the iFuse Implant System.

Figure 2 – New Treatment Pathway with iFuse Implant System



3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Introduction of the technology (iFuse Implant System) in the existing health system would require minimal changes. The surgeons and the theatre staff would need to be trained on the procedure. Diagnosis and non-surgical management of these patients is most effectively performed with a multidisciplinary team composed of interventional pain management, interventional radiology, physiotherapy, and surgeons. The existing NHS care delivery model for low back pain already emphasizes the multidisciplinary team (MDT) model.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

There are no additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies, infrastructure or capital investment will be used alongside the technology (iFuse Implant System) for the claimed benefits to be realized.

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

It is anticipated that adoption of the technology (iFuse Implant System) will results in lower utilization of diagnostic tests (MRI, CT scans, diagnostic injections) and treatment (medications, physiotherapy, injections, RFA, and surgery) for patients with chronic lower back pain due to SI joint dysfunction that are not correctly diagnosed. If patients with chronic lower back pain are appropriately screened for SI joint dysfunction, these patients with SI joint dysfunction can then be appropriately treated resulting in lower costs and better outcomes. A decision analytic model has been developed and published showing a savings of $3,100 a patient when the SI joint is considered in the evaluation and treatment of chronic low back pain. Cost savings are, in part, driven by a reduction in the provision of inappropriate surgery. There is an online calculator available through this article where costs for the various diagnostic/treatment steps can be inserted and the model

can be run to provide a user with a relevant and customized output. [Polly 2016[28]]

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

It is not anticipated that the NHS would disinvest in any particular facility or technology. Rather, including the diagnosis and treatment of SI joint dysfunction in patients presenting with chronic lower back pain will result in an overall lower utilization of health care resources. This lower utilization of health care resources will come from the correct identification and cost-effective treatment of patients with SI joint dysfunction.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use. [YES]
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity. [YES]
- quality systems (ISO 13485) certificate (if required). [YES]

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

CE Mark Allowed November 11, 2010.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Country	Date of Registration / Approval
Australia	December 2013
Canada	May 2015; Withdrawn in Nov 2017
Hong Kong	April 2014
Israel	February 28, 2014
Korea	Class I approved April 2, 2015 Class II approved Oct. 28, 2015 Class III iFuse approved Feb 25, 2016
Malaysia	September 9, 2015
New Zealand	July 2013
Saudi Arabia	February 29, 2016
Singapore	October 19, 2015
Taiwan	May 6, 2016
USA	November 26, 2008

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

The product is already available commercially in the UK.

4.5 If the technology has been launched in the UK provide information on the use in England.

CE Mark Allowed November 11, 2010. The following table lists use of iFuse Implant System to date in the UK.

Type	Hospital (Town)	Cases
Irish NHS	Cappagh National Orthopaedic Hospital (Dublin)	1
Irish NHS	Tallaght Hospital (Dublin)	1
NHS	Chase Farm Hospital (Barnet)	12
NHS	Cheshire and Merseyside TC (Warrington)	13
NHS	Epsom Hospital (Epsom)	1
NHS	Frimley Park (Frimley)	31
NHS	Glasgow Royal - Queen Elizabeth (Glasgow)	6
NHS	Guys Hospital (London)	2
NHS	John Radcliffe Hospital (Oxford)	2
NHS	King Edward VII's Hospital (London)	1
NHS	Llandough Hospital (Cardiff)	45
NHS	Nuffield Orthopaedic Centre (Oxford)	5
NHS	Princess Alexandra Hospital (Harlow)	7
NHS	Princess Royal Hospital (Haywards Heath)	1
NHS	Queen Elizabeth University Hospital (Glasgow)	20
NHS	Queens Medical Centre (QMC) (Nottingham)	5
NHS	RNOH - Royal National Orthopaedic Hospital (Stanmore)	21
NHS	Royal Berkshire Hospital (Reading)	3
NHS	Royal London Hospital (London)	5
NHS	Royal Orthopaedic Hospital (Birmingham)	1
NHS	Royal Sussex County Hospital (Brighton)	1
NHS	Royal Victoria Hospital (Belfast)	3
NHS	Sailsbury District General Hospital (London)	0
NHS	Southampton General Hospital (Hampshire)	1
NHS	Stepping Hill (Stockport)	3
NHS	Sussex Ortho Treatment Centre (Haywards Heath)	2
NHS	The Montefiore Hospital, Spire (Brighton)	7

Type	Hospital (Town)	Cases
NHS	Warrington Hospital (Warrington)	5
NHS	William Harvey Hospital (Ashford)	2
Private	Spire Cardiff (Cardiff)	2
Private - Aspen	The Holly Private Hospital (Essex)	2
Private - BMI	BMI The Harbour Hospital (Poole)	3
Private – BMI	BMI Winterbourne Hospital (Dorchester)	2
Private - BMI Group	BMI Ridgeway Hospital (Swindon)	4
Private – Circle	Circle Reading Hospital (Reading)	8
Private – HCA	London Bridge Hospital – HCA (London)	13
Private - Mater Private Group	Mater Hospital (Dublin)	16
Private – Nuffield	The Vale Hospital – Nuffield (Cardiff)	41
Private - Ramsay Healthcare	Ramsay New Hall Hospital (London)	32
Private - Ramsay Healthcare	Ramsay Rivers Hospital (Sawbridgeworth)	1
Private - Spire	Spire Southampton (Southampton)	2
Private – Spire	Spire Cheshire (Warrington)	6
Private – Spire	Spire Clare Park (Farnham)	16
Private – Spire	Spire Regency Hospital (Macclesfield)	8
Private – Spire	Spire Roding (London)	2

5 Ongoing studies

Two Ongoing Clinical Trials (LOIS and SALLY)

LOIS (NCT02270203) is a prospective multicentre single-arm study conducted at 12 sites in the US. LOIS is continued long-term follow-up from two prospective trials (INSITE and SIFI) conducted in the US. The goal of LOIS is to confirm the long-term safety and efficacy of minimally invasive SI joint fusion (SIJF) using the iFuse Implant. The paragraph below summarizes a recently submitted manuscript.

[redacted]

SALLY (NCT03122899) is a prospective multicentre single-arm study of patients with SI joint pain who undergo SIJF using iFuse-3D, a modification of iFuse with interstices designed to promote bone on-growth and through-growth. The target sample size is 50 patients and the study has follow-up at 3, 6, 12, 24 and 60 months. The study is currently in the enrolment phase.

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Results from two clinical studies will be published in the next 12 months.

iMIA (NCT01741025) is a prospective randomized controlled trial of SIJ fusion vs. conservative management. Previously results from 6 and 12-month follow-up were published. 24-month follow-up is complete. A manuscript describing results will be submitted in December 2017. Study results show persistent

improvement from baseline in all parameters in the SIJ fusion group, including pain, disability, quality of life, active straight leg raise test, global comparisons to baseline, walking distance, satisfaction and desirability of having surgery again. No new adverse events of interest have occurred since publication of the 12-month manuscript [Dengler 2017b[29]].

LOIS (NCT02270203) is a prospective multicentre single-arm study conducted at 12 sites in the US. LOIS is continued long-term follow-up from two prospective trials (INSITE and SIFI) conducted in the US. The goal of LOIS is to confirm the long-term safety and efficacy of minimally invasive sacroiliac joint fusion (SIJF).

[redacted]

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

SI-BONE is not aware of any ongoing clinical trials of iFuse Implant or iFuse-3D in the UK.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

SI joint dysfunction is a condition that predominantly affects women, possibly due to two overall reasons: 1) differences in anatomic structure between women and men and 2) SI joint needs to expand during parturition. In prospective clinical trials, approximately 2/3 of the subjects were women. This gender distribution is consistent and well supported by the clinical literature.

Global anatomic differences

Females

- increased lumbar lordosis
- increased sacral slope
- knees more valgus
- hips more varus
- morphology of pelvis

Soft tissues

Females

- more elastin in collagen (more flexible)
- differences in proportion of type I and Type II muscle fibers

Pregnancy & Postpartum Pelvic Girdle Pain

- Overall weight gain is 9-18 kg
- Shift in centre of gravity (more cephalad and anterior)
- Increased lordosis of lumbar spine
- Anterior rotation of the pelvis on the hips
- Stretch of the abdominal muscles
- Increased activity of the erector spinae muscles
- Attenuation/damage of pelvic floor muscles (bears weight of uterus)
- Changes to ligaments structure of the pelvis after pregnancy/parturition may be permanent, which can impact the normal function of the SI joint.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

It is not anticipated that there will be any equality issues relating to the assessment of the technology that may require special attention.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

-NA-

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

SI-BONE continuously monitors the published literature for the presence of studies related to SI joint pain or SI joint fusion. SI-BONE has kept a database of published literature relevant to the SI joint since 2012. All newly identified studies are added to the database. SI-BONE is not aware of any ongoing studies of SIJ fusion other than those previously published and those sponsored by SI-BONE. Nonetheless, a Medline search of "sacroiliac joint AND (fusion OR arthrodesis) was performed to identify all relevant published works. No additional publications of interest were found.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

SI-BONE is not aware of any unpublished studies that speak to the safety and efficacy of SI joint fusion using iFuse Implant System. Unpublished manuscripts from LOIS and iMIA are described above.

7.2 Study selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B1 Selection criteria used for published studies

Inclusion criteria	
Population	Patients with sacroiliac joint dysfunction that is a direct result of sacroiliac joint disruption and/or degenerative sacroiliitis.
Interventions	Minimally invasive SI joint fusion with the iFuse Implant
Outcomes	Clinical outcomes (pain, disability, quality of life), operative measurements, measures of satisfaction, measures of adverse event rates
Study design	Prospective and retrospective
Language restrictions	None, though only Medline was searched. Other databases may index journals that are not peer-reviewed.
Search dates	2009 to present
Exclusion criteria	
Population	None
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

There are 53 known peer-reviewed published articles (PDFs can be found here: https://app.box.com/v/iFuse-pubs) that report/analyse iFuse Implant System data.

Two additional publications deal with iFuse data in different ways and are described and referenced below.

- **MenMuir – Int J Spine Surg 2017**[30]: reports 4 patients treated with iFuse that are later revised with SImmetry Sacroiliac Joint Fusion (Zyga, Inc., Minnetonka, MN, USA).
- **Kancherla – Asian Spine J 2017**[31]: Retrospective, case series of 45 patients treated with minimally invasive SI joint fusion. Of the 45 patients, 36 were treated with iFuse Implants and 9 with SAMBA System (Medical Designs, LLC, Sioux Falls, SD, USA), but the outcomes are not broken out by implant/device.

Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Patients with sacroiliac joint dysfunction that is a direct result of sacroiliac joint disruption and/or degenerative sacroiliitis.
Interventions	Minimally invasive SI joint fusion with the iFuse Implant
Outcomes	Clinical and operative measurements
Study design	Prospective and retrospective
Language restrictions	None
Search dates	
Exclusion criteria	
Population	
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

There are two known iFuse article submissions currently under review at the respective journals, and one article in progress with submission planned for later in 2017.

- [redacted]

[redacted]

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

Table B3 List of relevant published studies

As of October 2017, there are 53 peer-reviewed, published iFuse articles (see details below). PDFs of articles can be found here: https://app.box.com/v/iFuse-pubs

iFuse Implant System Publications (53)

Level I	Randomized Controlled Trials	7
Level II/IIb	Prospective, Multicenter	6
Level III	Comparison	5
Level IV	Case Series	17
Reviews	Systematic, Meta-analysis	3
Economics	Cost-effective, Productivity	5
Other	Complications, Survivorship, etc.	7
Biomechanics	Stability, ROM, Implant Placement	3

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
LEVEL I – Randomized Controlled Trials				
Polly 2017 (2-year results)[32] **Randomized Controlled Trial, Multicenter (19 sites in the US)** *Prior publications:* • Polly 2016 (Does SIJ block predict SIJ fusion)[33]; • Polly 2015 (1yr results)[34]; • Whang 2015 (6mo results)[35]	Investigation of Sacroiliac Fusion Treatment (INSITE) NCT01681004	Patients ages 21 to 70 with SI joint dysfunction that is a direct result of SI joint disruption and/or degenerative sacroiliitis, and who failed to achieve acceptable symptom relief after a minimum of 6 months of conservative care.	MIS SI Joint fusion with iFuse Implant (n=148)	Non-surgical management (NSM) (n=46) NSM designed to be consistent with current US practices – consisted of pain medications as directed by the site investigator, physical therapy (PT) following American Physical Therapy Association (APTA) guidelines, intraarticular SI joint steroid injections and radiofrequency (RF) ablation of sacral nerve roots, all of which were delivered in a stepwise fashion and tailored to each individual patient's needs.

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Dengler 2017b (1-year results of RCT)[29] **Randomized Controlled Trial, Multicenter (9 spine care clinics in Europe, 4 countries)** *Prior publications*: • Dengler 2016 (referred leg pain)[36]; • Sturesson 2016 (6mo results)[37] [redacted]	iFuse Implant System® Minimally Invasive Arthrodesis (iMIA) NCT01741025	Patients ages 21 to 70 with SI joint dysfunction that is a direct result of SI joint disruption and/or degenerative sacroiliitis, and who failed to achieve acceptable symptom relief after a minimum of 6 months of conservative care.	MIS SI Joint fusion with iFuse Implant (n=52)	Conservative Management (CM) (n=51) CM designed according to the European guidelines for the diagnosis and management of pelvic girdle pain. CM consisted of (1) optimization of medical therapy, (2) individualized physical therapy (PT) that focused on mobilization and stabilization exercises for control and stability, and (3) adequate information and reassurance of the patient as part of a multifactorial treatment.
LEVEL II/IIb – Prospective, Multicenter				
Duhon 2016 (2-year results)[38] **Prospective, Single-arm, multicentre (26 sites in the US)** *Prior publications*: • Duhon 2015 (1yr results)[39]; • Duhon 2013 (6mo interim results)[40]	Sacroiliac Joint Fusion With iFuse Implant System (SIFI) NCT01640353	Patients ages 21 to 70 with SI joint dysfunction that is a direct result of SI joint disruption and/or degenerative sacroiliitis, and who failed to achieve acceptable symptom relief after a minimum of 6 months of conservative care.	MIS SI Joint fusion with iFuse Implant (n=172)	-NA-

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Cher 2015 (improvement in health state utility after SIJ fusion compared to normal populations)[41]	Sacroiliac Joint Fusion With iFuse Implant System (SIFI) NCT01640353	[see SIFI above]	MIS SI Joint fusion with iFuse Implant (n=172)	Normal individuals who participated in a nationally representative cross-sectional survey (National Health Measurement Study [NMHS], n=3844)
Capobianco 2015 (PPGP sub-analysis of SIFI)[42]	Sacroiliac Joint Fusion With iFuse Implant System (SIFI) NCT01640353	[see SIFI above]	MIS SI Joint fusion with iFuse Implant: Women whose pain began in the peripartum period (PPGP, n=20)	MIS SI Joint fusion with iFuse Implant: Women no PPGP (n=100) Men (n=52)
Dengler 2017a (pooled analysis of INSITE, iMIA, and SIFI)[43]	INSITE NCT01681004 iMIA NCT01741025 SIFI NCT01640353	[see INSITE, iMIA, and SIFI above]	MIS SI Joint Fusion with iFuse Implant (n=326)	Non-surgical management (NSM/CM) (n=97)
LEVEL III – Comparative				
Graham Smith 2013[44]	-NA-	Patients undergoing open or minimally invasive SI joint fusion at 7 US centres	MIS SI Joint Fusion with iFuse Implant (n=114)	Open SI Joint Fusion (n=149)
Ledonio 2014a[45]	-NA-	Patients undergoing open or minimally invasive SI joint fusion at 1 US centre	MIS SI Joint Fusion with iFuse Implant (n=22)	Open SI Joint Fusion (n=22)

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Ledonio 2014b[46]	-NA-	Patients undergoing open or minimally invasive SI joint fusion at 2 US centres	MIS SI Joint Fusion with iFuse Implant (n=17)	Open SI Joint Fusion (n=22)
Spain 2017 (4yr revision rate)[47]	-NA-	Patients undergoing SI joint fixation with screws or SI joint fusion with iFuse Implant System at a single US centre	MIS SI Joint Fusion with iFuse Implant (n=263)	SI Joint Fixation with screws (n=29)
Vanaclocha 2017 (6yr follow-up)[48]	-NA-	Patients undergoing SI joint fusion with iFuse Implant System, conservative management or RF ablation of the SI joint at a single Spanish centre	MIS SI Joint Fusion with iFuse Implant (n=27)	Conservative Management (CM, n=63) SI Denervation (Radiofrequency Ablation, RF, n=47)
LEVEL IV – Case Series (only 4 key publications listed, see Section 7.3.2 for all others)				
Bornemann 2016 (2yr follow-up)[49]	-NA-	Patients undergoing SI joint fusion with iFuse Implant System at a single German centre	MIS SI Joint Fusion with iFuse Implant (n=24)	-NA-
Sachs 2016 (3yr follow-up)[50]	-NA-	Patients undergoing SI joint fusion with iFuse Implant System at 7 US centres	MIS SI Joint Fusion with iFuse Implant (n=107)	-NA-
Rudolf 2014 (5yr follow-up)[51]	-NA-	Patients undergoing SI joint fusion with iFuse Implant System at a single US centre	MIS SI Joint Fusion with iFuse Implant (n=17)	-NA-

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Vanaclocha 2014 (up to 4yr follow-up)[52]	-NA-	Patients undergoing SI joint fusion with iFuse Implant System at a single Spanish centre	MIS SI Joint Fusion with iFuse Implant (n=24)	-NA-
REVIEWS				
Lingutla 2016[53]	-NA-	Systematic Review	MIS SI Joint Fusion (Open n=92, MIS n=315)	Open SI joint fusion
Heiney 2015[54]	-NA-	Systematic Review	MIS SI Joint Fusion using a lateral transarticular approach (18 articles = 15 iFuse, 3 screws; 432 subjects = 368 iFuse, 64 screws)	SI joint fusion using screws
Zaidi 2015[55]	-NA-	Systematic Review	SI Joint fusion (n=131 open, n=299 MIS)	Open SI joint fusion
OTHER – Complications, Survivorship (revision), *in vivo* testing				
MacBarb 2017 (*in vivo* testing of iFuse Implant integration into bone)[56]	-NA-	*in vivo* sheep study		-NA-
Cher 2014 (4yr survivorship / revision)[57]	-NA-	Administrative database review	MIS SI Joint Fusion with iFuse Implant (n=11,388)	-NA-
Miller 2013 (complications)[58]	-NA-	Administrative database review	MIS SI Joint Fusion with iFuse Implant (n=5,319)	-NA-

Table B4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Dengler, Julius for the iMIA Study Group (risk factors for continued opioid use) [redacted]	iFuse Implant System® Minimally Invasive Arthrodesis (iMIA) NCT01741025	[see iMIA above]	MIS SI Joint fusion with iFuse Implant (n=52)	Conservative Management (CM) (n=51)
Darr, Emily for the LOIS study group (3yr follow-up) [redacted]	Long-Term Follow-Up in INSITE/SIFI (LOIS) NCT02270203	[see INSITE and SIFI above]	MIS SI Joint fusion with iFuse	-NA-
Dengler, Julius for the iMIA Study Group (2-year results of RCT) [redacted]	iFuse Implant System® Minimally Invasive Arthrodesis (iMIA) NCT01741025	[see iMIA above]	MIS SI Joint fusion with iFuse Implant (n=52)	Conservative Management (CM) (n=51)

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

Several case series publications [Bornemann 2016[59], Manfre 2014[60], Sachs 2014[61], Scheyerer 2014[62], Schroeder 2013[63], Gaetani 2013[64], Cummings 2013[65], Sachs 2013[66], Rudolf 2013[67], Kim 2013[68], Sachs 2012[69], Lokietek 2012[70], Rudolf 2012[71]] were not included because the results were similar to

the RCT and prospective trials (rapid and sustained clinically significant improvement). See also Section 7.8.

Three biomechanical studies were not listed because they don't include clinical outcomes. However, results demonstrate the iFuse Implant performs as it was designed:

- The implants rapidly stabilize the SI joint and stabilization is maintained after cycles [Lindsey 2014[72]]
- There is flexibility in the transarticular placement of the implants across the joint with similar results [Soriano-Baron 2015[73]]
- Stabilization of the SI joint with the implants has very little effect on the lumbar spine range of motion [Lindsey 2015[74]]

Several publications involving economic calculations have been published listed below and utilized in Section C – Economics Evidence. These are excluded from this section because they do not describe clinical outcomes.

- Frank 2016[75] – work intensity in SI joint fusion and lumbar microdiscectomy
- Saavoss 2016 – worker productivity after MIS SI joint fusion
- Polly 2016 – ignoring SI joint pathology in LBP patients is costly
- Cher 2016 – cost-effectiveness of MIS SI joint fusion with iFuse
- Garber 2015 – surgeon work effect involved in MIS SI joint fusion

Several other non-iFuse specific publications involving economic calculations are listed below.

- Ackerman 2013[76] – US Medicare Population, comparison cost of non-operative care vs. MIS SI joint fusion
- Ackerman 2014a[77] – US Medicare Population, cost of non-operative care for SI joint pathology
- Ackerman 2014b[78] – US Commercial Payor Population, cost of non-operative care for SI joint pathology
- Ackerman 2014c[79] – US Commercial Payor Population, comparison cost of non-operative care vs. MIS SI joint fusion

7.4 Summary of methodology of relevant studies

There are more than 50 peer-reviewed published articles on the iFuse Implant System (www.si-bone.com/results). While all of the publications demonstrate consistent outcomes and results, the tables in this section focus on 6 key publications:

- INSITE – randomized controlled trial in the US [Table B5a]
- iMIA – randomized controlled trial in Europe [Table B5b]
- SIFI – prospective trial in the US [Table B6a]
- Pooled Analysis – patient-level data pooled analysis of INSITE, iMIA, and SIFI [Table B6b]
- LOIS – prospective trial with longer term follow-up of INSITE and SIFI patients [Table B6c]
- Vanaclocha 2017[48] – retrospective results comparing patients treated with conservative management, SI denervation (RF ablation), and iFuse, with follow-up out to 6 years [Table B6d]

INSITE, iMIA, SIFI, and LOIS are industry-sponsored multicentre trials with study protocols. All trials were run and overseen by SI-BONE clinical affairs. All trials underwent 100% source verification. CT scans were read by 1-3 independent radiologists. The pooled analysis combines patient-level data from INSITE, iMIA, and SIFI.

Vanaclocha et al.[48] is a retrospective case series of interest because it includes patients with the same disease whose insurance companies denied more aggressive care. Therefore, a substantial proportion of patients were forced to undergo conservative treatment. The study provides an interesting "natural history" experiment.

Most remaining studies were retrospective, did not undergo source verification or were missing important assessments or outcomes. However, these studies generally show results very consistent with the above-referenced publications.

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table B5a Summary of methodology for randomised controlled trials

Study name	**INSITE** (NCT01681004)
Objectives	To compare the safety and effectiveness of SI joint fusion using the iFuse Implant vs. NSM in patients with degenerative sacroiliitis (DS) and/or sacroiliac dysfunction (SD).
Location	19 sites in the United States
Design	Multicenter, randomized controlled clinical trial with crossover component
Duration of study	2 years
Sample size	N=148 (102 iFuse, 46 NSM)
Inclusion criteria	1. Age 21-70 at time of screening 2. Patient has buttock or lower back pain for >6 months inadequately responsive to conservative care 3. Diagnosis of sacroiliac joint disruptions or degenerative sacroiliitis based on ALL of the following: a. Patient has pain at or close to the posterior superior iliac spine (PSIS) with possible radiation into buttocks, posterior thigh or groin and can point with a single finger to the location of pain (Fortin Finger Test/Fortin 1997[80]), and b. Patient has at least 3 of 5 physical examination maneuvers specific for the SI joint, and c. Patient has improvement in lower back pain numeric rating scale (NRS) at 30 or 60 minutes of at least 50% after injection of local anesthetic into affected SI joint(s) and NRS immediately prior to screening diagnostic SI joint block of at least 5 on a scale of 0-10*, and d. One or more of the following: i. SI joint disruptions: 1. Asymmetric SI joint widening on any radiographic study (e.g., X-ray, MRI or CT scan), or 2. Leakage of contrast on diagnostic arthrography ii. Degenerative sacroiliitis: 1. Radiographic evidence of SI joint degeneration, including sclerosis, osteophytes, subchondral cysts, or vacuum

	phenomenon on CT or plain film, or 2. Due to prior lumbosacral spine fusion 4. Baseline Oswestry Disability Index (ODI) score of at least 30% 5. Baseline average SI joint pain score of at least 50 on 0-100 mm visual analog scale 6. Patient has signed study-specific informed consent form 7. Patient has the necessary mental capacity to participate and is physically able to comply with study protocol requirements
Exclusion criteria	1. Severe back or hip pain due to other causes, such as lumbar disc degeneration, lumbar disc herniation, lumbar spondylolisthesis, lumbar spinal stenosis, lumbar facet degeneration, lumbar vertebral body fracture, femoral acetabular impingement or hip osteoarthritis. Patients with back pain VAS ratings more than 50 should be carefully considered – they may have excessive residual competing pain to qualify. 2. Other known sacroiliac pathology such as: a. Sacral dysplasia b. Inflammatory sacroiliitis (e.g., ankylosing spondylitis or other HLA-associated spondyloarthropathy) c. Tumor d. Infection e. Acute fracture f. Crystal arthropathy 3. History of recent (<1 year) major trauma to pelvis 4. Previously diagnosed osteoporosis (defined as prior T-score < -2.5 or history of osteoporotic fracture) or prior use of drug therapy for osteoporosis. Patients who have not had a DEXA in last 2 years and who meet the osteoporosis screening criteria identified by the National Osteoporosis Foundation should be screened for osteoporosis with DEXA and excluded if the T score is < -2.5. 5. Osteomalacia or other metabolic bone disease 6. Chronic rheumatologic condition (e.g., rheumatoid arthritis, lupus) 7. Any condition or anatomy that makes treatment with the iFuse Implant System infeasible 8. Chondropathy 9. Known allergy to titanium or titanium alloys 10. Use of medications known to have detrimental effects on bone quality and soft-tissue healing 11. Prominent neurologic condition that would interfere with physical therapy 12. Current local or systemic infection that raises the risk of surgery 13. Patient currently receiving or seeking short- or long-term worker's compensation related to the SI joint or low back pain, currently receiving disability remuneration related

	to SI joint or low back pain, and/or currently involved in injury litigation related to the SI joint or low back pain. 14. Currently pregnant or planning pregnancy in the next 2 years 15. Patient is a prisoner or a ward of the state. 16. Known or suspected drug or alcohol abuse 17. Diagnosed uncontrolled psychiatric disease (e.g., schizophrenia, major depression, personality disorders) that could interfere with study participation 18. Patient is participating in an investigational study or has been involved in an investigational study within 3 months prior to evaluation for participation other than the VaReFi study sponsored by SI-BONE, Inc. 19. Fibromyalgia
Method of randomisation	2:1 randomization Final sample size determined via Bayesian interim analysis
Method of blinding	None The implant is radiopaque. Blinding would have required sham surgery (which investigators refused to consider) and would have required patients to avoid seeing their X-rays/CTs, which clearly show radiopaque implants.
Intervention(s) (n =) and comparator(s) (n =)	iFuse Implant (n=102) NSM (n=46)
Baseline differences	None
Duration of follow-up, lost to follow-up information	24 months
Statistical tests	**Primary endpoint**: comparison of proportion meeting composite endpoint (improvement of SI joint pain of at least 20 points without reoperation/reintervention, device-related serious adverse event or neurologic adverse event) at 6 months. Proportions were compared using exact Bayesian distribution. **Secondary endpoints**: comparison of change scores for SIJ pain and Oswestry Disability Index using t tests or repeated measures analysis of variance.
Primary outcomes (including scoring methods and timings of assessments)	By month 6, 84 of 102 SIJF subjects (82%, 95% posterior credible interval [CI] 74-89%) and 12 of 46 NSM subjects (26%, 14-41%) met the study's primary success endpoint. The intent-to-treat difference in success rates was 55% (95% CI 40-69%), representing a >3-fold difference in success rate, and the posterior probability that the success rate was higher in the SIJF group was >0.9999.
Secondary outcomes (including scoring methods and timings of assessments)	In the SIJF group, the **mean SIJ pain score** improved from 82.3 at baseline to 30.1 at 6-month follow-up, 28.6 at 12 months and 26.7 at 24 months, corresponding to improvements from baseline of 52.3, 53.7and 55.4 points, respectively (all p<.0001 from baseline). In the NSM group, mean SIJ pain improved from 82.2 to 70.3 at 6 months (12.2-point improvement). Combining all time points up to month 6, the improvement in VAS SIJ improvement was 38.2 points greater for the SIJF group compared to the NSM group (p<.0001, repeated measures analysis of variance). In the

	SIJF group, mean ODI decreased from 57.2 at baseline to 29.9, 28.3 and 28.7 at months 6, 12 and 24, representing improvements of 27.4, 28.9 and 28.4 points, respectively (p<.0001). In the NSM group, mean ODI decreased by only 4.6 points at 6 months (p=0.0537).

Table B5b Summary of methodology for randomised controlled trials

Study name	**iMIA** (NCT01741025)
Objectives	To compare the safety and effectiveness of SI joint fusion using the iFuse Implant System vs. conservative management in patients with chronic, disabling SI Joint pain.
Location	9 spine care clinics (4 countries) in Europe
Design	Prospective multicentre randomized controlled trial
Duration of study	24 months
Sample size	103 (target sample size 100)
Inclusion criteria	1. Age 21-70 at time of screening 2. 2. Patient has lower back pain for >6 months or >18 months for pregnancy induced lower back pain. 3. Diagnosis of the SI joint as the primary lower back pain generator based on ALL of the following: a. Patient has pain at or close to the posterior superior iliac spine (PSIS) with possible radiation into buttocks, posterior thigh or groin and can point with a single finger to the location of pain (Fortin Finger Test), and b. Patient has at least 3 of 5 physical examination maneuvers specific for SI joint pain (Compression, Östgaard 4P (Thigh Thrust), Patrick's (Faber), Long Ligament Test, and Gaenslen's), and c. Patient has improvement in lower back pain NRS of at least 50% of the pre-injection NRS score after fluoroscopic controlled injection of local anesthetic into affected SI joint(s) (including previous documented test <6 months ago) 4. Baseline Oswestry Disability Index (ODI) score of at least 30% 5. Baseline lower back pain score of at least 50 on 0-100 point VAS 6. Patient has signed study-specific informed consent form Patient has the necessary mental capacity to participate and is physically able to comply with study protocol requirements.

Exclusion criteria	1. Severe lower back pain due to other causes, such as lumbar disc degeneration, lumbar disc herniation, lumbar spondylolisthesis, lumbar spinal stenosis, lumbar facet degeneration, and lumbar vertebral body fracture 2. Sacroiliac pathology caused by auto-immune disease (e.g. ankylosing spondylitis) and/or neoplasia (e.g. benign or malignant tumor) and/or crystal arthropathy 3. History of recent (<1 year) fracture of the pelvis with documented malunion, non-union of sacrum or ilium or any type of internal fixation of the pelvic ring. 4. Spine surgery during the past 12 months. 5. Previously diagnosed or suspected osteoporosis (defined as prior T-score <-2.5 or history of osteoporotic fracture) 6. Documented osteomalacia or other metabolic bone disease 7. Any condition or anatomy that makes treatment with the iFuse Implant System infeasible 8. Known allergy to titanium or titanium alloys 9. Use of medications known to have detrimental effects on bone quality and soft-tissue healing 10. Prominent neurologic condition that would interfere with physical therapy 11. Current systemic infection or local infection at the SI joint 12. Currently pregnant or planning pregnancy in the next year 13. Known or suspected drug or alcohol abuse 14. Diagnosed psychiatric disease (e.g., schizophrenia, major depression, personality disorders) that could interfere with study participation Patient is participating in an investigational study or has been involved in an investigational study within 3 months of surgery.
Method of randomisation	Randomization was stratified by study site and whether SIJ pain is related to pregnancy
Method of blinding	The study was not blinded
Intervention(s) (n =) and comparator(s) (n =)	SIJF: n=52 Conservative management (CM): n=51
Baseline differences	No relevant differences
Duration of follow-up, lost to follow-up information	24-month follow-up was obtained in 90% in both groups
Statistical tests	Changes in continuous measures compared with unpaired t tests. Differences in proportions compared with Fisher's test.
Primary outcomes (including scoring methods and timings of assessments)	Primary outcome: improvement in low back pain as rated by visual analog scale (0-100 scale) at 6 months. LBP improvement at 6 months was significantly larger in the SIJF group vs. CM (43.3 points vs. 5.7 points, difference of 38 points, p<.0001). Improvement in LBP after SIJF persisted at month 24 (mean improvement 43.6 points, 34 points higher

	than CM, p<.0001); pain scores were statistically superior through month 24.
Secondary outcomes (including scoring methods and timings of /assessments)	Improvements in **leg pain** paralleled those seen in LBP, with minimal improvements in the CM group (1.4 points at 6 months and 10 points at 24 months) and large improvements (30 points and 32 points) in the SIJF group. In the CM group mean **ODI** improved minimally at 6 and 24 months (by 5.6 and 10.3 points, respectively); in contrast, mean ODI improved rapidly in the SIJF group (by 26 points at both 6 and 24 months). At month 6, 79% of subjects in the SIJF group had an improvement in LBP by at least 20 VAS points vs. 22% in the CM group. 24 months after SIJF, 77% had at least a 20-point improvement vs. 29% in the CM group. Threshold 24-month improvements for ODI occurred in 63% vs. 28% of SIJF and CM groups, respectively. Similar patterns were observed for **EQ-5D**, with large changes in the SIJF group at 6 and 24 months (0.37 and 0.39 points) and smaller changes in the CM group (0.09 and 0.15 points). Mean **Zung depression score**, which was just above normal at baseline, showed no improvement in the CM group and a 6-point improvement in the SIJF group, which difference persisted at 24 months. All across-group comparisons reported here had p-values of <.001. **Active straight leg raise test (ASLR)**, which assesses functional capacity related to the SIJ, showed no significant improvement in the CM group but large and superior improvements after SIJF (p<.0001 compared to baseline and p<.0001 compared to CM). Superior improvement in the number of positive physical examination findings was also observed (p<.0001). Additional outcomes included self-reported walking distance, global comparison to baseline, satisfaction levels and desirability of having the same treatment again, all of which were superior after SIJ fusion compared to CM. At month 24, work status in the SIJF group was significantly improved compared to baseline (p=.001).

Table B6a Summary of methodology for observational studies

Study name	**Sacroiliac Joint Fusion With iFuse Implant System (SIFI)** (NCT01640353)
Objective	The objective of this study is to document the safety and effectiveness of the iFuse Implant System for SI joint fusion in patients with degenerative sacroiliitis (DS) and/or sacroiliac dysfunction (SD).
Location	26 sites in the United States
Design	Multicenter, prospective clinical trial of the iFuse Implant System for SI joint fusion.
Duration of study	24 months
Patient population	Patients with sacroiliac joint dysfunction that is a direct result of sacroiliac joint disruption and/or degenerative sacroiliitis.
Sample size	N=172
Inclusion criteria	1. Age 21-70 at time of screening 2. Patient has lower back pain for >6 months inadequately responsive to conservative care 3. Diagnosis of sacroiliac joint disruption or degenerative sacroiliitis based on ALL of the following: a. Patient has pain at or close to the posterior superior iliac spine (PSIS) with possible radiation into buttocks, posterior thigh or groin and can point with a single finger to the location of pain (Fortin Finger Test), and b. Patient has at least 3 of 5 physical examination maneuvers specific for the SI joint (see Table 3), and c. Patient has improvement in lower back pain numeric rating scale (NRS) of at least 50% after injection of local anesthetic into affected SI joint(s), and d. One or more of the following: i. SI joint disruption: 1. Asymmetric SI joint widening on X-ray or CT scan, or 2. Leakage of contrast on diagnostic arthrography ii. Degenerative sacroiliitis: 1. Radiographic evidence of SI joint degeneration, including sclerosis, osteophytes, subchrondral cysts, or vacuum phenomenon on CT or plain film, or 2. Due to prior lumbosacral spine fusion 4. Baseline Oswestry Disability Index (ODI) score of at least 30% 5. Baseline SI joint pain score of at least 50 on 0-100 mm visual analog scale [0=no pain, 100=worst imaginable pain] 6. Patient has signed study-specific informed consent form 7. Patient has the necessary mental capacity to participate and is physically able to comply with study protocol requirements

Exclusion criteria	1. Severe back pain due to other causes, such as lumbar disc degeneration, lumbar disc herniation, lumbar spondylolisthesis, lumbar spinal stenosis, lumbar facet degeneration, and lumbar vertebral body fracture [Patients with severe lower back pain in addition to SI joint pain may be candidates for SI joint fusion using the iFuse Implant System. However, severe lower back pain may confound assessments of SI joint pain; hence, these patients will be excluded from the study.] a. Other known sacroiliac pathology such as: b. Sacral dysplasia c. Inflammatory sacroiliitis (e.g., ankylosing spondylitis or other HLA-associated spondyloarthropathy) d. Tumor e. Infection f. Acute fracture g. Crystal arthropathy 2. History of recent (<1 year) major trauma to pelvis 3. Previously diagnosed osteoporosis (defined as prior T-score <-2.5 or history of osteoporotic fracture). Patients meeting the osteoporosis screening criteria identified by the National Osteoporosis Foundation (NOF) should be 4. screened for osteoporosis with DEXA. 5. Osteomalacia or other metabolic bone disease 6. Chronic rheumatologic condition (e.g., rheumatoid arthritis) 7. Any condition or anatomy that makes treatment with the iFuse Implant System infeasible 8. Chondropathy 9. Known allergy to titanium or titanium alloys 10. Use of medications known to have detrimental effects on bone quality and soft-tissue healing 11. Prominent neurologic condition that would interfere with physical therapy 12. Current local or systemic infection that raises the risk of surgery 13. Patient currently receiving or seeking worker's compensation, disability remuneration, and/or involved in injury litigation. 14. Currently pregnant or planning pregnancy in the next 2 years 15. Patient is a prisoner or a ward of the state. 16. Known or suspected drug or alcohol abuse 17. Diagnosed psychiatric disease (e.g., schizophrenia, major depression, personality disorders) that could interfere with study participation 18. Patient is participating in an investigational study or has been involved in an investigational study within 3 months prior to evaluation for participation
Intervention(s) (n =)	172
Baseline differences	none

How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Prospective follow-up clinic visits at 1, 3, 6, 12, 18 and 24 months after iFuse Treatment. At 2 years, follow-up was obtained in 149 subjects (87%).
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	**Primary Clinical Endpoint** – Subject success, a composite endpoint, defined as all of the following: improvement in VAS SI joint pain by ≥20 mm, lack of device-related serious adverse events, absence of neurologic worsening and absence of surgical re-intervention (see protocol Section 4.1 for details) at 6 months **Primary Radiographic Endpoint** – Occurrence of at least 30% apposition of bone to both the iliac and sacral sides of at least 2 of 3 iFuse devices on 12-month CT scan
Secondary outcomes (including scoring methods and timings of assessments)	• Improvement in VAS SI joint pain [scale 0-100] (baseline, 1, 3, 6, 12, 18 and 24 months) • Improvement in Oswestry Disability Index (ODI) [scale 0.100] (baseline, 1, 3, 6, 12, and 24 months) • Improvement in quality of life (SF-36 PCS [scale 0-100] and EQ-5D [scale 0-1]) (baseline, 6, 12, and 24 months) • Narcotic medication use (1, 3, 6, 12, 18, and 24 months) • Time to full ambulatory status (baseline, 1, 3, 6, 12, 18 and 24 months) • Return to work (baseline, 1, 3, 6, 12, 18, and 24 months) • Satisfaction (6, 12, and 24 months) • CT scan (screening, 12 months) • Pelvic x-ray (screening, discharge, 3, 6, and 24 months) • Rate of serious adverse events (procedure, discharge, 1, 3, 6, 12, 18, and 24 months)

Table B6b Summary of methodology for observational studies

Study name	**Pooled Analysis of INSITE, iMIA, and SIFI**
Objective	The aim of this study was to identify predictors of outcome of conservative and minimally invasive surgical management of pain originating from the sacroiliac joint (SIJ).
Location	INSITE (US), iMIA (Europe), SIFI (US)
Design	A pooled patient-level analysis of two multicenter randomized controlled trials and one multicenter single-arm prospective trial.
Methods	Pooled individual patient data from the three trials and used random effects models with multivariate regression analysis to identify predictors for treatment outcome separately for conservative and minimally invasive surgical treatment. Outcome was measured using visual analogue scale (VAS), Oswestry Disability Index (ODI), and EuroQOL-5D (EQ-5D).
Patient population	Patients with sacroiliac joint dysfunction that is a direct result of sacroiliac joint disruption and/or degenerative sacroiliitis.
Sample size	423 patients assigned to either: nonsurgical management (NSM, n=97) or SIJF (n=326) between 2013 and 2015.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	All patients were prospectively followed
Statistical tests	We applied random effects models, performed using the nlme and lme4 R packages, that used appropriate covariance structures to take into account individual patient characteristics (fixed effects) as well as repeated measures and site-level factors (random effects). Both univariate and multivariate regression techniques were used, including interaction terms. Outcomes assessed in a single trial only were not evaluated. As both RCTs allowed crossover from NSM to SIJF after month 6, the treatment effect in the NSM cohorts was estimated using only 1, 3, and 6-month data. Models regarding patient age and pain duration used values grouped by quartiles. Opioid use was defined as continuous daily opioid use, including oral medication and/or transdermal application.
Primary outcomes (including scoring methods and timings of assessments)	SI joint pain using visual analogue scale (VAS); Oswestry Disability Index (ODI); EuroQOL-5D (EQ-5D).

Table B6c Summary of methodology for observational studies

Study name	**Long-Term Follow-Up in INSITE/SIFI (LOIS)** (NCT02270203)
Objective	The purpose of this study is to evaluate the long-term safety and effectiveness of SI joint fusion using the iFuse Implant System in patients with degenerative sacroiliitis (DS) and/or sacroiliac joint disruptions (SD).
Location	US sites
Design	This study is extended follow-up from two completed multicenter prospective US clinical trials. All participants have already undergone the surgical procedure of interest (SI joint fusion with iFuse Implant System). The two ongoing trials are: INSITE and SIFI.
Duration of study	3 years on LOIS (5 years post-op)
Patient population	
Sample size	
Inclusion criteria	See INSITE & SIFI
Exclusion criteria	See INSITE & SIFI
Intervention(s) (n =) and comparator(s) (n =)	103 iFuse
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	proactive
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	**Subject Success:** Composite endpoint of success defined as improvement in VAS (Visual Analog Scale) recorded at SIFI or INSITE Baseline VAS back pain score by ≥20 mm; Absence of device-related SAE (Serious Adverse Events); Absence of neurological worsening related to the sacral spine, and absence of surgical re-intervention on the target SI joint(s). **Radiographic (CT) apposition of bone to sacral and iliac sides of implant:** Proportion of subjects (with CT) who had at least 30% apposition of bone to sacral and iliac sides in at least 2 of 3 iFuse implants.

Secondary outcomes (including scoring methods and timings of assessments)	• VAS (Visual Analog Scale) – Improvement in VAS (Visual Analog Scale), SI joint pain at follow-up visits. • Oswestry Disability Index (ODI) Questionnaire – Improvement in Oswestry Disability Index (ODI) at follow-up visits. • Improvement in quality of life (QOL) – Improvement in quality of life as measure by EQ-5D Questionnaire at follow-up visits. • Non-working subjects returning to work – Proportion of non-working subjects who return to work • CT scans showing bridging bone – Proportion of CT scans that show bridging bone across the SI joint at 5 years post-operatively • SAE (Serious Adverse Events) occurrence rate – Occurrence rate of serious adverse events.

Table B6d Summary of methodology for observational studies

Study name	**Vanaclocha – Neurosurgery 2017**[48]
Objective	To determine responses to conservative management (CM), SIJ denervation, and SIJF in patients with SIJ pain unresponsive to CM.
Location	Single neurosurgical clinic in Spain
Design	Comparative retrospective case series.
Duration of study	6 years
Patient population	Patients with suspected SI joint pain. 423 adults (age, 21-75 years) evaluated in the neurosurgical department between January 2007 and November 2015.
Sample size	137 patients with SIJ pain
Inclusion criteria	Chronic SIJ pain was diagnosed based on 3 or more months of pain in the lumbosacral area immediately medial and below the posterior superior iliac spine (PSIS) with possible radiation into the buttocks, posterior thigh, or groin (minimum pain score of 5 on the 0 to 10 visual analog scale [VAS]) with no focal neurological signs, an Oswestry Disability Index (ODI) score of at least 30%, a positive Fortin finger test, and positive findings on at least 3 of 8 physical examination maneuvers that stress the SIJ (FABER test, Patrick's test, thigh thrust, distraction test, compression test, Gaenslen test, sacral thrust, and Yeoman test). Diagnosis was confirmed with the occurrence of at least 50% pain relief after image-guided intraarticular injection of contrast and local anesthetic (bupivacaine 1.5 mL) into the SIJ. The sacroiliac (SI) infiltration procedure was considered confirmed if contrast was observed on fluoroscopy inside the SIJ.
Exclusion criteria	Patients were excluded if they had severe residual pain due to other causes, other SI pathology (trauma, fracture, tumor, ankylosing spondylitis, osteitis condensans ilii, SIJ arthropathy, Reiter's syndrome, psoriatic arthritis, enteric arthritis), recent major trauma, pregnancy, drug abuse, lack of definitive proof that pain originated in the SIJ, acute pain improvement after SIJ infiltration of <50%, lumbar spine instability (e.g., spondylolisthesis), osteoporosis, or other

	metabolic bone disease. All patients also underwent cross-sectional imaging (*e.g.*, CT or MRI) to rule out other common causes of low back or hip pain.
Intervention(s) (n =) and comparator(s) (n =)	SIJF with iFuse (n=27) SI Denervation (n=47) Conservative Management (CM, n=63)
Baseline differences	No differences in age, sex, body mass index, smoker, cigarettes per day, % of bilateral SIJ pain. SIJF patients: • More likely to have lower pain duration • More likely to have pain with driving, sitting or standing • Less likely to have prior lumbar fusion (less diagnostic confusion) Conservative patients: • Higher pain duration • More likely to have pain with activity • More likely to have prior lumbar fusion See Table 1 of published study.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Any patient receiving CM visited the clinic every 6 months. Any patient receiving an interventional treatment returned to clinic 1 month after the treatment and every 6 months thereafter. **CM group** – 63 patients had 1-yr follow-up, and 2-, 3-, 4-, 5-, and 6-yr follow-up was available in 52, 43, 34, 23, and 16 patients, respectively. (Mean follow-up = 44 months) **SI denervation group** – 47 had 1-yr follow-up and further follow-up (2, 3, 4, 5, and 6-yr) was available in 41, 33, 23, 6, and 2 patients. (Mean follow-up = 39 months) **SIJF group** – 27 patients had 1-year follow-up and further follow-up (2, 3, 4, 5, and 6-yr) was available in 24, 20, 15, 6, and 1 patients. (Mean follow-up = 41 months).
Statistical tests	Repeated measures analysis of variance for continuous scores. Fisher test for comparison of proportions.
Primary outcomes (including scoring methods and timings of assessments)	SI Joint pain as measured with visual analog scale (VAS, 0-10).
Secondary outcomes (including scoring methods and timings of assessments)	Oswestry Disability Index (ODI, scale 0-100). Pain medication use. Work status, focusing on whether the patient eventually received government payments due to partial or complete inability to work.

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

LOIS is long-term prospective follow-up from both INSITE and SIFI (two US sponsored prospective trials). 3-year results from LOIS are anticipated to be published within the next 4 months.

Dengler's pooled analysis combines results from INSITE, iMIA, and SIFI.

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

Nearly all studies enrolled patients using an identical diagnostic algorithm, including history, physical examination (5 structured diagnostic manoeuvres that stress the SI joint and reproduce pain), and a confirmatory diagnostic SI joint block with local anaesthetic performed under fluoroscopic or CT guidance. All studies used cross-sectional imaging to rule out other potential cases of low back pain. All studies enrolled patients with either degenerative sacroiliitis (i.e., SIJ degeneration due to osteoarthritis) or SI joint disruption (e.g., due to prior trauma or childbirth). All studies used substantially similar methods for performing the implantation procedure. Most studies used similar methods of assessment, including pain and disability scores. Most studies showed a female predominance, which is consistent with prior reports of SI joint pain. All studies were performed in a similar outpatient spine clinic setting. In one study (Schroeder), patients had SIJ pain as a result of long fusion of the spine to the sacrum for deformity. All other studies enrolled unselected patients with SIJ pain. Female predominance was found in all studies.

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Subgroup analyses were prespecified in the clinical investigational protocols for INSITE, iMIA, and SIFI. The focus of Dengler's pooled analysis study [Dengler 2017a[43]] was to report prespecified and exploratory subgroup analyses from all 3 prospective trials.

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

In INSITE, 442 patients were screened for participation, of which 159 (37.8%) were randomized. 11 subjects withdrew between enrolment and treatment. See complete INSITE patient flow diagram in section 7.4.6 below.

In iMIA (conducted in Europe), screen failure logs were not captured. 109 subjects were enrolled, of which 6 withdrew after randomization and prior to treatment. See complete iMIA patient flow diagram in section 7.4.6 below.

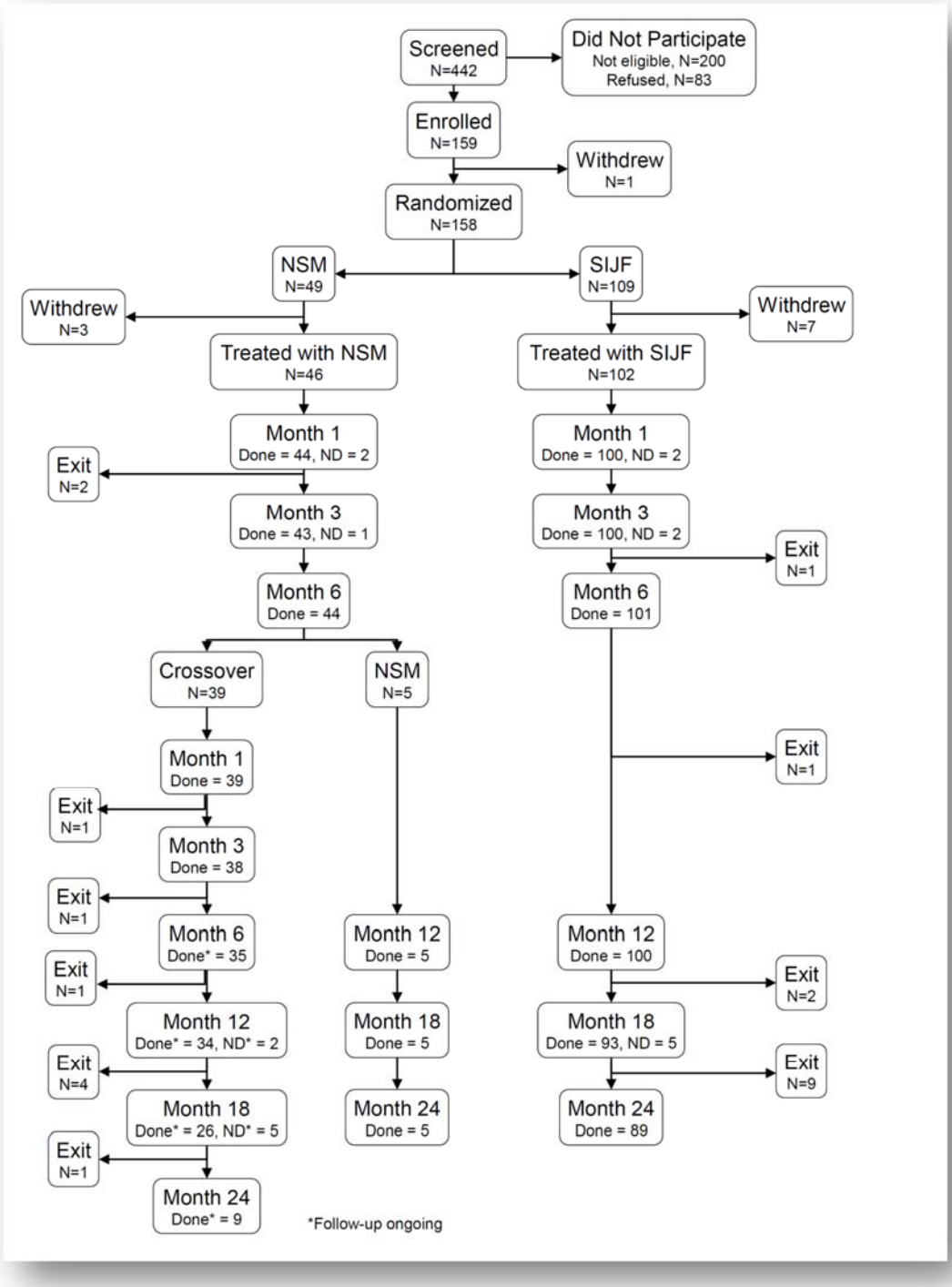
7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

INSITE 2-year

Lost to follow-up or voluntary withdrawal is very common in long-term prospective trials. In INSITE, 13 of 102 subjects randomized to SIJ fusion withdrew prior to month 24. Nine were lost to follow-up despite multiple efforts to contact them, 1 was withdrawn by the site principle investigator (PI) for drug-seeking behavior, 2 were withdrawn as a result of site termination from the study, and 1 died due from a fatal myocardial infarction. One site was terminated after 12-month subject visits were complete due to persistent non-compliance with the study protocol. In the NSM arm, 6-month (primary endpoint) follow-up was available in 44/46 (96%); two subjects withdrew voluntary consent to participate. After the 6-month visit, crossover was allowed and 39 of 44 (89%) still participating crossed over to SIJ fusion. Crossover occurred 1 to 12 months following the 6-month NSM visit. NSM subjects crossing over to SIJ fusion more than 6 months after the 6-month

visit were not required to have visit 2 years after crossover surgery. Follow-up in the crossover group is shown in the chart below.

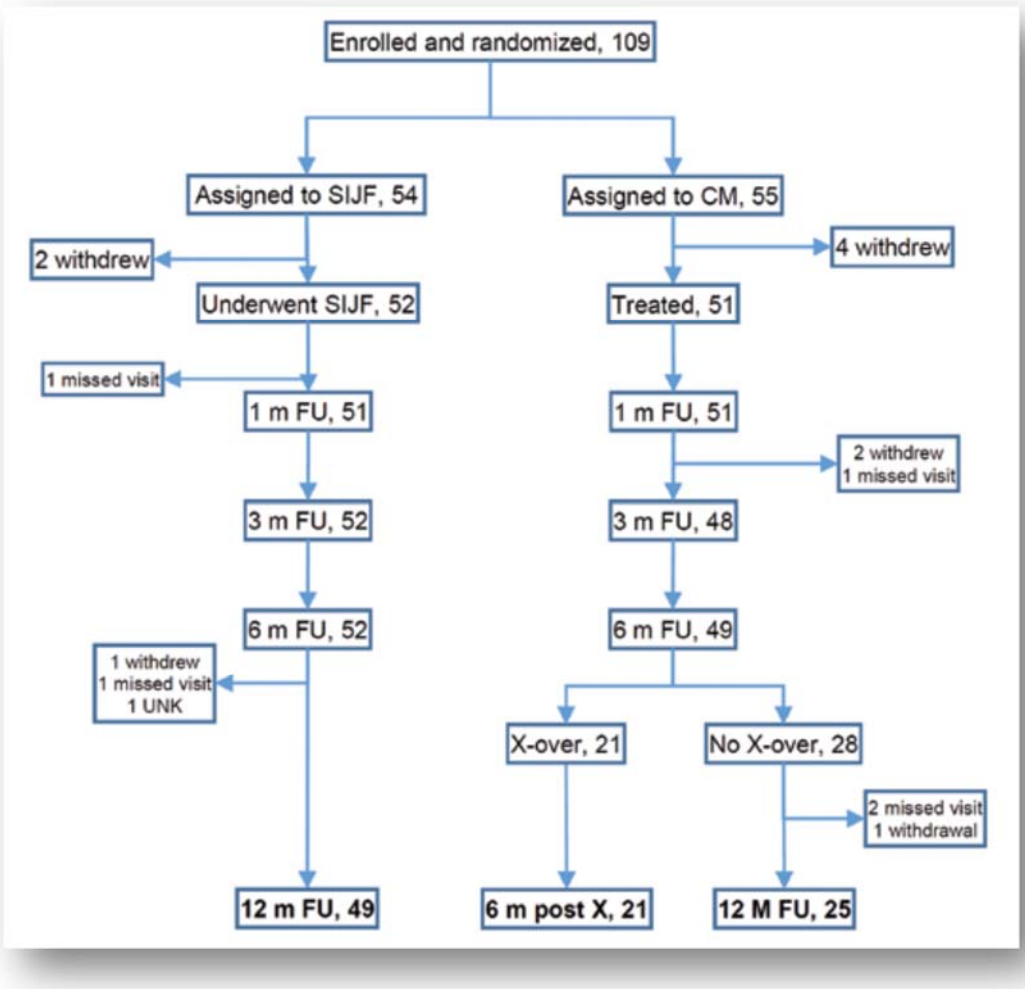
Figure 3 – INSITE Patient Flow



iMIA 1-year

Patient Flow Diagram through 1-year follow-up [Dengler 2017b[29]] is shown below. Like the INSITE randomized controlled trial, iMIA allowed patients randomized to conservative management to crossover to SIJF (iFuse) after the 6-month visit. Of the 49 CM patients with 6-month follow-up, 21 (43%) crossed over.

Figure 4 – iMIA Patient Flow (1-year)



iMIA 2-year

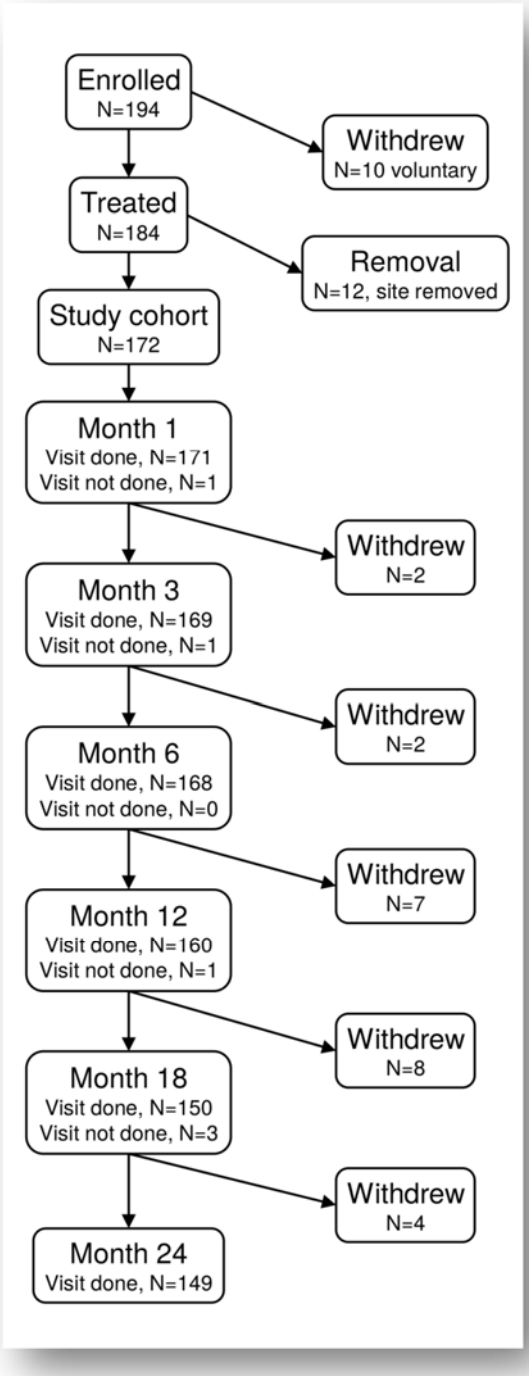
[redacted]

[redacted]

SIFI 2-year

Patient flow through 2 years in SIFI is shown below [Duhon 2016[38]].

Figure 6 – SIFI Patient Flow



Vanaclocha 2017 (CM, SI Denervation, SIJF)[48]

Conservative management, initially offered to all patients, included (1) counselling for smoking cessation and weight control, (2) physiotherapist consultation regarding chronic pain behavior avoidance, and (3) use of nonsteroidal anti-inflammatory agents (indomethacin, naproxen sodium, or ibuprofen). Physiotherapy was stopped after 3 months if no improvement was seen.

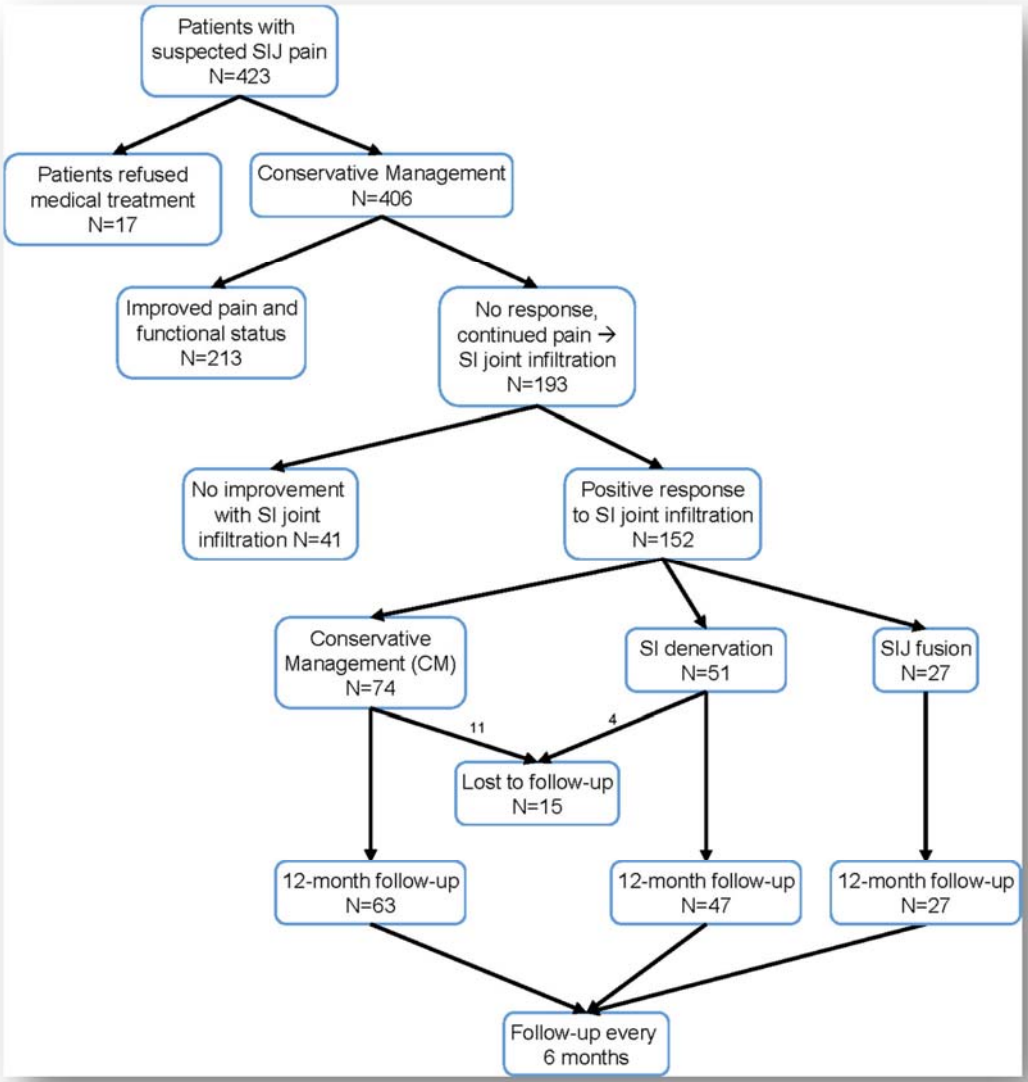
If CM failed to provide pain or disability relief within 6 months, patients were offered intraarticular SIJ steroid infiltrations (dexamethasone, 4 mg; betamethasone, 6 mg), which were performed under light sedation and fluoroscopic guidance (Figure 1, left). Patients showing little improvement in SIJ pain were re-evaluated for other sources of pain and excluded from analysis.

Patients with continued pain and disability were offered the following interventions:

- SI Denervation – radiofrequency ablation of the posterior sensory rami of L4. L5, S1, S2, and S3. Lesions were placed at L4, L5, and at various locations circumferentially near the S1, S2, and S3 branches, with target temperatures of 90◦ for 90 seconds. All procedures were performed in the outpatient setting, and no patient was hospitalized.
- SIJ Fusion with the iFuse Implant – performed in an inpatient setting under general anaesthesia and using dual-arm fluoroscopy with implantation of porous triangular titanium implants. Typically, 3 implants were placed across each treated SIJ. Patients were discharged the day after the procedure.

Patient flow diagram for Vanaclocha 2017 is shown below.

Figure 7 – Vanaclocha's Study Patient Flow



7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table B7a Critical appraisal of randomised control trials

Study name	**Investigation of Sacroiliac Fusion Treatment (INSITE)** NCT01681004	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomization was obtained through a password protected website. Randomization was stratified by study center. Comparison of baseline characteristics confirms successful randomization.
Was the concealment of treatment allocation adequate?	-NA-	INSITE was not a blinded study. Implants are radiopaque; any patient seeing her X-ray or CT scan would be immediately unblinded. For this reason, study blinding was deemed impossible.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline characteristics were evenly distributed across treatments. Prognostic indicators were not known when the study was begun.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	INSITE was not a blinded study. Knowledge of which treatment could have affected study results. However, most study assessments were carried out by unconflicted study coordinators and study results were highly consistent across outcomes.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Follow-up was high in both groups.

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All study outcomes were reported in manuscripts.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary efficacy endpoint was reported using intent-to-treat methods. The dropout rate by month 6 was low.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B7b Critical appraisal of randomised control trials

Study name	iFuse Implant System® Minimally Invasive Arthrodesis (iMIA) NCT01741025	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Randomization was obtained through a password protected website. Randomization was stratified by study center. Comparison of baseline characteristics confirms successful randomization.
Was the concealment of treatment allocation adequate?		iMIA was not a blinded study. Implants are radiopaque; any patient seeing her X-ray or CT scan would be immediately unblinded. For this reason, study blinding was deemed impossible.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		Baseline characteristics were evenly distributed across treatments. Prognostic indicators were not known when the study was begun.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		iMIA was not a blinded study. Knowledge of which treatment could have affected study results. However, most study assessments were carried out by unconflicted study coordinators.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		Follow-up was high in both groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?		All study outcomes were reported in manuscripts.

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		The 6-month primary efficacy endpoint was evaluated using available data. 6-month follow-up was available in 100% of subjects who underwent SIJ fusion and 49/51 (96%) of subjects undergoing CM. Missing data analysis would have had very little impact on study results, since score improvements in the CM group were very small compared to large improvements in the SIJ fusion group.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B7c Critical appraisal of prospective trials

Study name	**Sacroiliac Joint Fusion With iFuse Implant System (SIFI)** NCT01640353	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	-NA-	Prospective single-arm trial
Was the concealment of treatment allocation adequate?	-NA-	-NA-
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline characteristics were evenly distributed across treatments. Prognostic indicators were not known when the study was begun.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	INSITE was not a blinded study. Knowledge of which treatment could have affected study results. However, most study assessments were carried out by unconflicted study coordinators.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Follow-up was high in both groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All study outcomes were reported in manuscripts.

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary efficacy endpoint was reported using intent-to-treat methods. The dropout rate by month 6 was low.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B8 Critical appraisal of observational studies

Study name: Vanaclocha – Neurosurgery 2017[48]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	All patients seen in clinic were tracked per standard processes
Was the exposure accurately measured to minimise bias?	Yes	It is very clear when patients have conservative management, surgery or RF ablation
Was the outcome accurately measured to minimise bias?	Yes	Visual analog pain scores and Oswestry Disability Index were assessed directly by patients
Have the authors identified all important confounding factors?	Yes	Part of the focus of the Vanaclocha 2017 manuscript was on potential confounders.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	There are no well-established confounders for response to SIJ fusion. Patients in the conservative group were more likely to have a history of lumbar fusion (which may explain why insurance coverage was denied). However, lumbar fusion itself is not a known risk factor for poor response to SIJ fusion.
Was the follow-up of patients complete?	Yes	Follow-up ended at the time of the study report. Mean follow-up was approximately 40 months.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Confidence intervals for comparisons of pain, disability and opioid use do not overlap. Consequently, p-values comparing response to treatment were very small. Observed were: Large improvement in SIJ pain in the SIJF group, with worsening of pain in the CM and RF groups. Large improvement in disability (ODI) in the SIJF group, with worsening of disability in the CM and RF groups. Large decrease in opioid use in the SIJF group with marked increases in the CM and RF groups.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Table B9 Outcomes from published and unpublished studies

Study name		INSITE	iMIA	SIFI
Size of study groups	Treatment	102	52	172
	Control	46	51	-
Study duration	Time unit	2 years	2 years	2 years
Type of analysis	Intention-to-treat /per protocol	ITT****	PP	ITT
Outcome	Name	Proportion meeting primary efficacy endpoint (improvement of at least 20 points in VAS SIJ pain, absence of device-related serious adverse event, absence of neurological worsening related to the lumbosacral nerve roots, and absence of surgical re-intervention for SIJ pain. ITT approach used.	-NA-	Proportion meeting primary efficacy endpoint (improvement of at least 20 points in VAS SIJ pain, absence of device-related serious adverse event, absence of neurological worsening related to the lumbosacral nerve roots, and absence of surgical re-intervention for SIJ pain. ITT approach used.
	Unit	%	-NA-	%
Effect size	Value	55%	-NA-	80.2%
	95% CI	40-69%	-NA-	73.9-85.7%
Statistical test	Type	Comparisons of proportions	-NA-	Proportion test
	p value	< 0.0001	-NA-	< 0.0001 compared to 35% null hypothesis

Outcome	Name	SIJ pain, difference across groups at 1, 3 and 6 months	Low back pain, difference across groups at 1, 3 and 6 months	SIJ pain, change from baseline at 24 months
	Unit	0-100 VAS	0-100 VAS	0-100 VAS
Effect size	Value	38.3 points**	37.3**	53.4***
	95% CI	31.3-45.4	29-45.5	48.9-57.9
Statistical test	Type	Repeated measures ANOVA	Repeated measures ANOVA	Paired t test
	p value	< 0.0001	< 0.0001	< 0.0001
Other outcome	Name	Oswestry Disability Index (ODI), difference across groups at 1, 3 and 6 months	Oswestry Disability Index (ODI), difference across groups at 3 and 6 months	Oswestry Disability Index (ODI), change from baseline at 24 months
	Unit	None (0-100 scale)		
Effect size	Value	18.0**	18.3**	24.5***
	95% CI	12.6-23.5	12.6-24.0	21.1-27.9
Statistical test	Type	Repeated measures ANOVA	Repeated measures ANOVA	Paired t test
	p value	< 0.0001	< 0.0001	< 0.0001

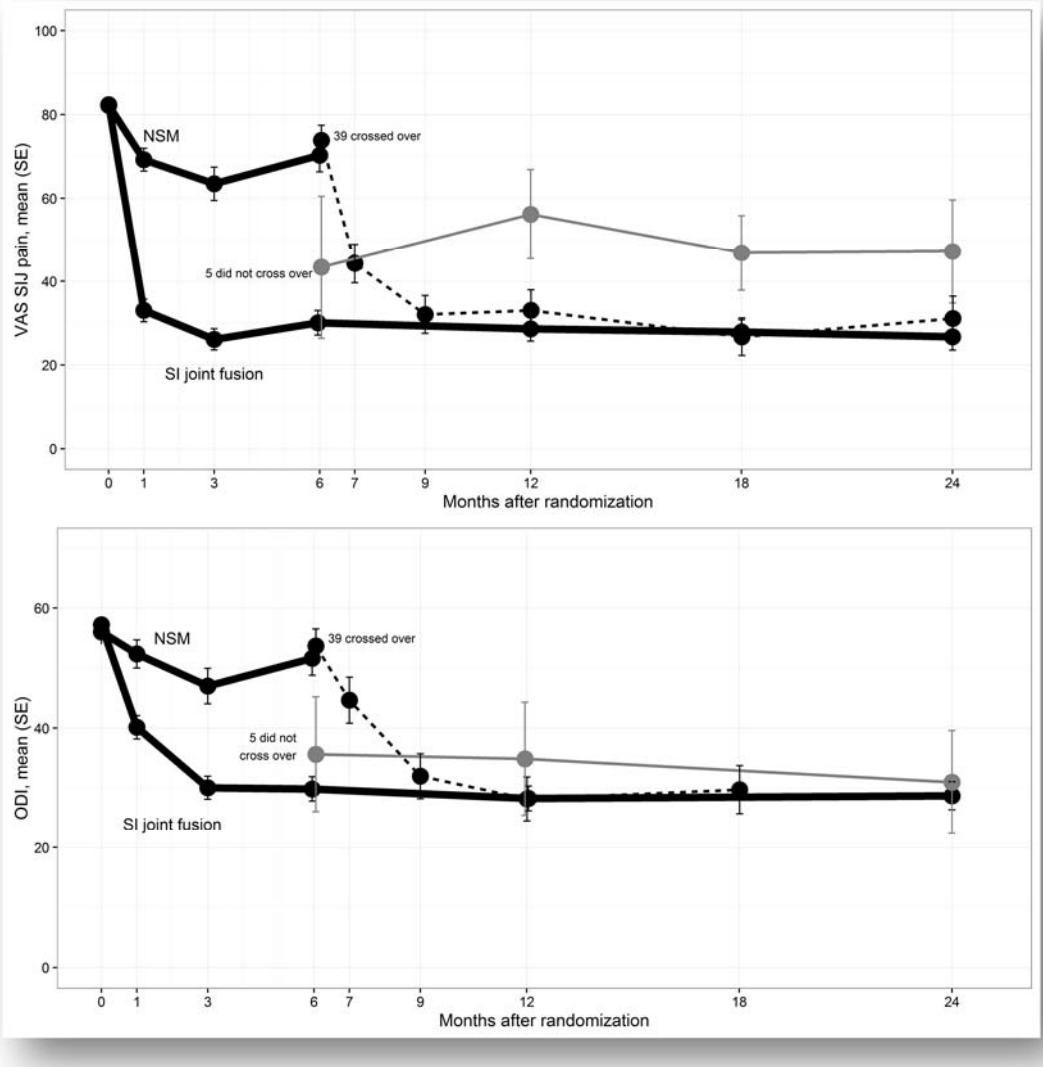
Comments	Marked homogeneity in treatment responses and effect sizes across studies. The following outcomes were positively affected by SIJ fusion: Pain Disability Quality of life (EuroQOL-5D and SF-36 [US studies only] Satisfaction and desirability of having procedure again Functional test (active straight leg raise test, assessed in iMIA only) Number of positive physical examination signs (iMIA only) Global comparison to baseline (iMIA only) Opioid use decreased in all 3 studies. The following outcomes were NOT improved to a clinically important degree in non-surgical management: Pain Disability Quality of life Satisfaction

* 6-month primary endpoint
** SIJF vs. non-surgical treatment
*** vs. baseline

INSITE

Figure from the INSITE 2-year publication showing the results of VAS SI Joint pain and ODI. Dark thick lines are those assigned to NSM or SIJF. Dotted line indicates NSM subjects who crossed over to surgery after the 6-month visit was complete. (Crossover after 6 months was allowed in the clinical investigational protocol.) Thin grey line indicates patients who did not cross over to surgery.

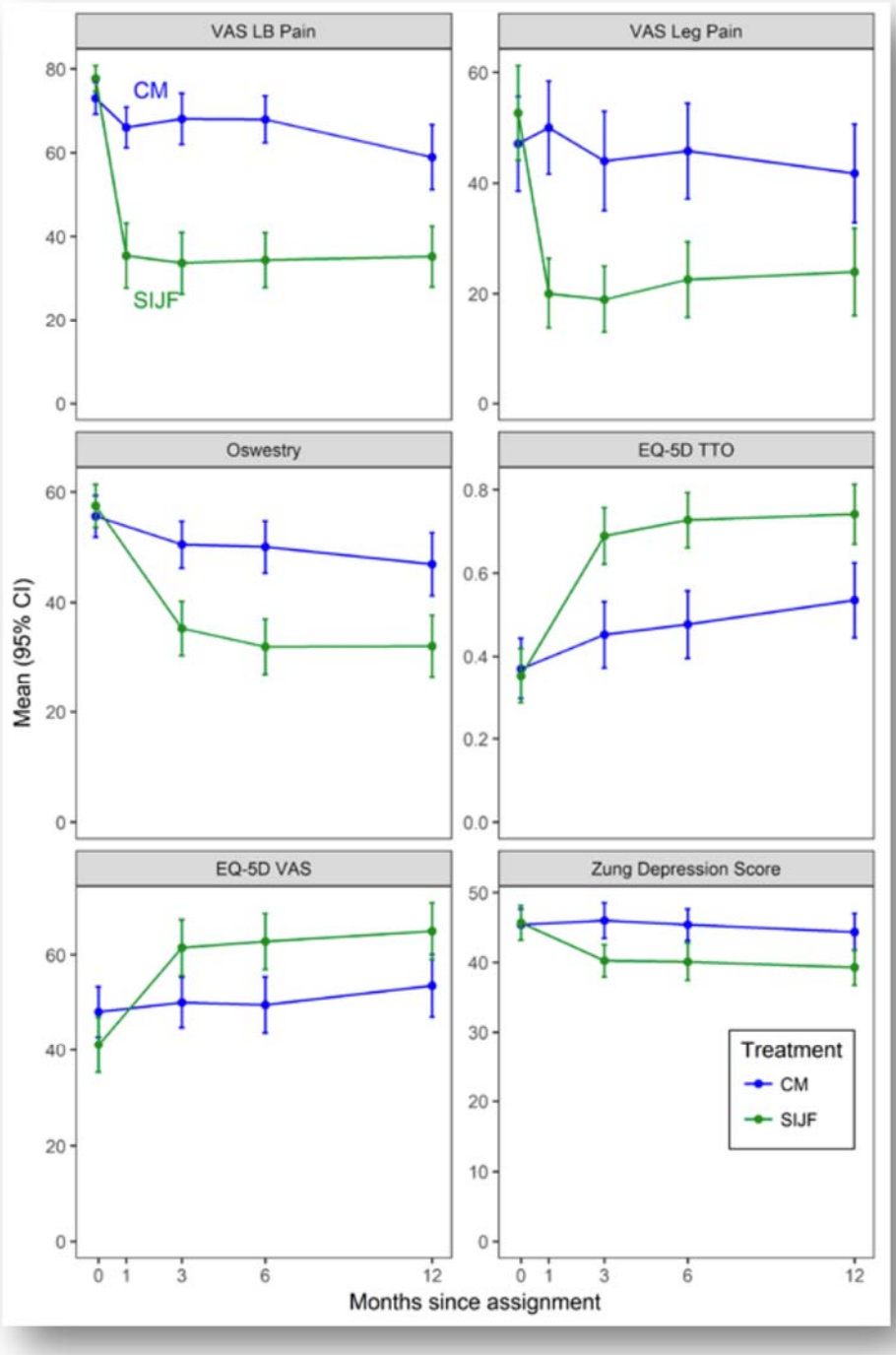
Figure 8 – INSITE 2-year Results



iMIA

1-year results from the publication, showing VAS Lower Back Pain, VAS Leg Pain, ODI, EQ-5D Time Trade-off, EQ-5D VAS, and Zung Depression Score. Blue line = Conservative Management, and Green line = SIJF (iFuse).

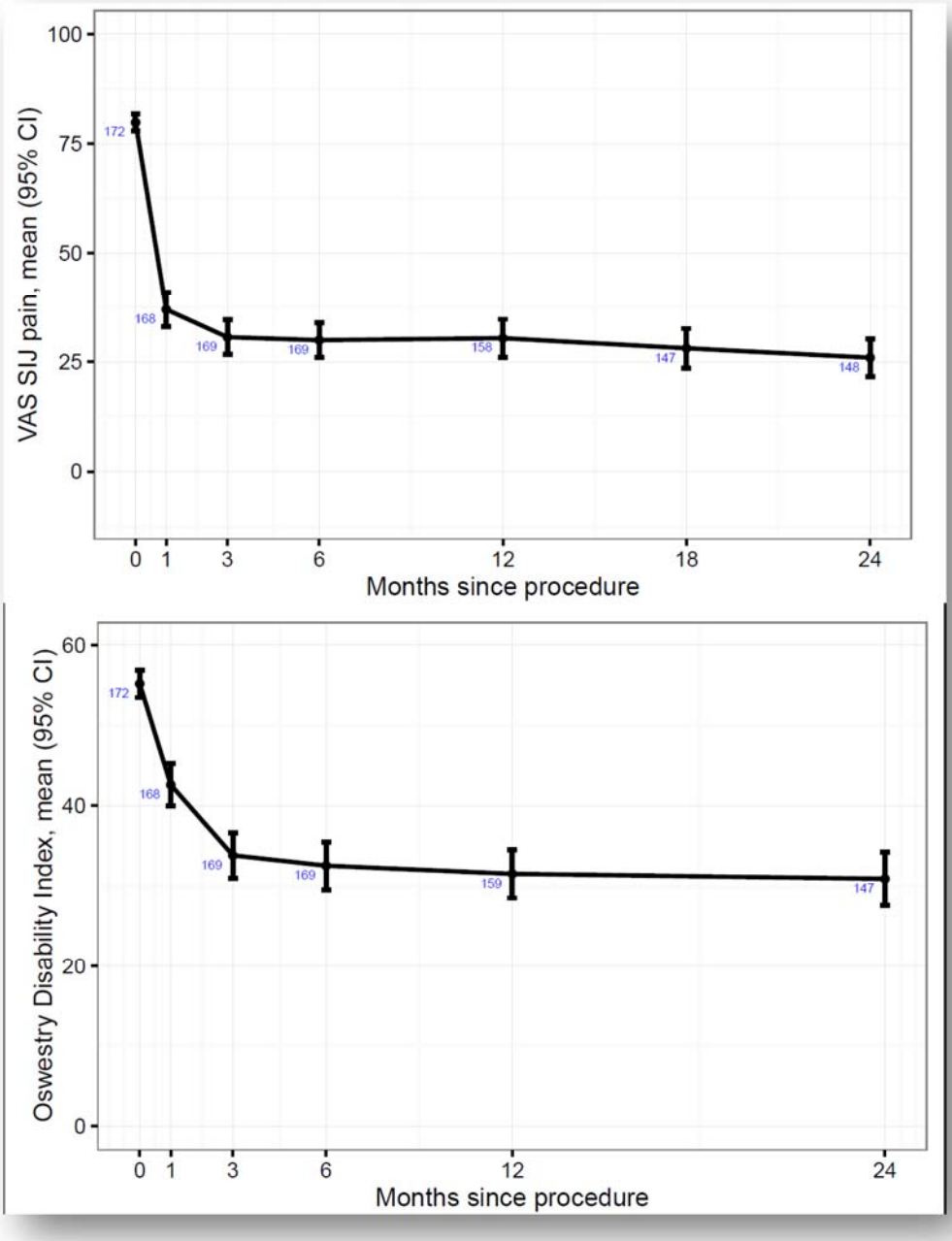
Figure 9 – iMIA 1-year Results



SIFI

2-year results from SIFI for VAS SI joint pain and ODI. Small blue numbers indicate the number of subjects at each timepoint.

Figure 10 – SIFI 2-year Results



7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

Intent-to-treat (ITT) was used for the primary analysis only in INSITE and SIFI. In INSITE and SIFI, the primary analysis was the proportion of patients with an improvement in VAS SIJ pain of at least 20 points without device-related neurologic adverse events, device-related serious adverse events and reoperation/reintervention. ITT was used to impute as failures any subject without study data at the primary endpoint time point. The proportion with missing data was low. Despite this, the difference in success rates between SIJF and non-surgical management was very large.

In iMIA, the primary analysis was the change in low back pain score at 6 months; only two CM patients had missing data. Had these subjects' values been imputed as 0 pain improvement, the calculated superiority of SIJF would have been even larger.

All other endpoints were evaluated using a standard "available data" approach.

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Adverse events were carefully assessed in the 3 prospective studies conducted by SI-BONE (INSITE, iMIA, SIFI). Studies were not necessarily powered to detect specific events.

In INSITE and iMIA, valid comparisons of adverse event rates across treatment (i.e., SIJF vs. non-surgical treatment) are possible only for the first 6 months after initial treatment. After month 6, subjects in the non-surgical

groups were allowed to crossover. Comparisons of adverse events after crossover from non-surgical to surgical treatment would not fairly assess the rate of adverse events in non-surgical treatment.

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

Important adverse events are defined as those probably or definitely related to the study procedure or treatment. In iMIA, events related to a pre-existing condition were also included to capture events related to conservative management. For both randomized trials, the number of individual events was very small, preventing accurate comparison of the two rates. In INSITE, the number of adverse events per subject during the first 6 months was similar across treatment groups (1.5/subject in SIJF vs. 1.3 per subject in NSM, p=.2253). In iMIA, there were 10 events in 9 SIJF subjects in first 6 months vs. 14 events in 13 CM subjects in the first 6 months. The mean number of events in the SIJF was slightly smaller than in the CM group (0.19 vs. 0.27, p=.0918).

Table B10a Adverse events across patient groups

Device, procedure or treatment-related adverse events in INSITE.

Body System	Event	SIJF, n*	Rate	NSM, n	Rate	P value	RR	CI
Injury / Procedural complication	incision numbness	0	(0%)	1	(2%)	0.6817	0.31	0.24-0.39
	incision drainage	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	wound hematoma	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	ilial fracture	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	revision - SIJ pain	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	neuropathic leg pain from guidepin	0	(0%)	1	(2%)	0.6817	0.31	0.24-0.39
	revision - neuropathy	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	urinary retention	2	(2%)	0	(0%)	0.8516	0.95	0-Inf
	nausea	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	infection	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	Neuropathy resolved with revision	0	(0%)	1	(2%)	0.6817	0.31	0.24-0.39
	stitch abscess	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	delayed wound healing	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	SIJ pain - ipsilateral	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	atrial fibrillation/respira failure	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
Musculoskeletal / Connective tissue	SIJ pain - ipsilateral	1	(1%)	5	(11%)	0.0176	0.34	0.22-0.52
	SIJ pain - contralateral	1	(1%)	1	(2%)	1.0000	0.46	0.11-1.89
	thigh pain	0	(0%)	1	(2%)	0.6817	0.31	0.24-0.39
	back pain	0	(0%)	2	(4%)	0.1766	0.30	0.24-0.39
	trochanteric bursitis	2	(2%)	0	(0%)	0.8516	0.95	0-Inf
	gluteus medius tear	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
Nervous System	fibromyalgia	0	(0%)	1	(2%)	0.6817	0.31	0.24-0.39
	worsened PE - left motor	0	(0%)	1	(2%)	0.6817	0.31	0.24-0.39
	buttock pain and burning	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
	worsened PE - knee	1	(1%)	0	(0%)	1.0000	0.63	0-Inf
General	flushing and sob post steroid inj	0	(0%)	1	(2%)	0.6817	0.31	0.24-0.39

*Number with event divided by number treated

Table B10b Adverse events across patient groups

Device, procedure or treatment-related adverse events in iMIA.

Body System	Event	iFuse*	Rate	NSM	Rate	P value	RR	CI	
Pelvic girdle	Contralateral SIJ pain	1	(2%)	0	(0%)	1	1.00	0-Inf	
Pelvic girdle	Haematoma at surgical site	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Pelvic girdle	Neural impingement by implant	1	(2%)	0	(0%)	1	1.00	0-Inf	
Pelvic girdle	neurogenic pain	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Pelvic girdle	pelvic gridle pain	1	(2%)	0	(0%)	1	1.00	0-Inf	
Pelvic girdle	Post-procedure hematoma	1	(2%)	0	(0%)	1	1.00	0-Inf	
Pelvic girdle	SI joint pain resulting in revision surgery	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Pelvic girdle	SIJ pain	3	(6%)	6		0.4664	0.68	0.41-1.14	
Hip	coxarthrosis	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Hip	hip pain	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Hip	pain unknown origin	1	(2%)	0	(0%)	1	1.00	0-Inf	
Hip	trochanteritis	1	(2%)	0	(0%)	1	1.00	0-Inf	
Low back	Back pain due to spondylolisthesis, spinal stenosis and possible adjacent segment degeneration	1	(2%)	0	(0%)	1	1.00	0-Inf	
Low back	Back pain of unknown cause	1	(2%)	0	(0%)	1	1.00	0-Inf	
Low back	Back pain related to spondylolisthesis and prior surgery	1	(2%)	0	(0%)	1	1.00	0-Inf	
Low back	Facet arthropathy	1	(2%)	0	(0%)	1	1.00	0-Inf	
Low back	Failure of spinal cord stimulator wire	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Low back	lumbar stenosis	1	(2%)	0	(0%)	1	1.00	0-Inf	
Other	Acute glaucoma	1	(2%)	0	(0%)	1	1.00	0-Inf	
Other	Carpal tunnel syndrome	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Other	Depression	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Other	fall resulting in burn	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Other	implant repositioning during procedure	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Other	infection	1	(2%)	0	(0%)	1	1.00	0-Inf	
Other	Medication overdose	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Other	Menometrorrhagia	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Other	Mental depression	0	(0%)	1	(2%)	0.9922	0.49	0.4-0.6	
Other	Morton's metatarsalgia	1	(2%)	0	(0%)	1	1.00	0-Inf	
Other	tingling both arms	1	(2%)	0	(0%)	1	1.00	0-Inf	
Other	Ulnar nerve entrapment	1	(2%)	0	(0%)	1	1.00	0-Inf	

*Number with event divided by number treated

A pooled analysis [Dengler 2017a[43]] of all three prospective trials (INSITE, iMIA and SIFI) summarized events in 326 subjects undergoing iFuse. Events were:

- 4 (1.2%) underwent early surgical revision. In each case, one implant was inadvertently placed into the sacral foramen causing radicular pain. In each case, pain resolved after repositioning of the implant.
- 9 (2.8%) underwent late revision surgery, typically done to address pain and sometimes associated with poor implant position.
- 8 (2.5%) had wound-related issues. 1 subject required surgical washout. All other subjects were treated with medical therapy and local wound care. No subject had implant removal due to bone infection.

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

iFuse Implant System has been used primarily (>90%) in the US. SI-BONE adheres to standard reporting practices for medical device reports (MDR) per 21 CFR 803. All MDRs are characterized by the chief medical officer and tracked in an internal database. The table below shows the number and rate of MDRs reported to FDA's MAUDE database from 2008 through September 2017. As a proportion of number of procedures in the US, the MDR rate is low.

Adverse Event	Count	% of Total Procedures	% of Adverse Events
Revision: Malpositioned-Nerve Impingement	297	1.06%	44.9%
Revision: Malpositioned-Short, wrong size or not across joint	101	0.36%	15.3%
Revision: Lucency/Halos	101	0.36%	15.3%
Revision: Insufficient Fixation	48	0.17%	7.3%
Revision: No pain relief	33	0.12%	5.0%
Revision: Other	30	0.11%	4.5%
Infection	13	0.05%	2.0%
Hematoma/Seroma/Bleeding	10	0.04%	1.5%
Guide pin cut/broken and left in patient	5	0.02%	0.8%
Embolism/Aneurysm/DVT	5	0.02%	0.8%
Pain Complaints (General)	4	0.01%	0.6%
Cardiac Incident	4	0.01%	0.6%
Pin Advancement/Binding/Cutting	2	0.01%	0.3%
Intraoperative Issues	2	0.01%	0.3%
Death	2	0.01%	0.3%
Off-Label	1	0.00%	0.2%
Broken pin/removal tip left in patient	1	0.00%	0.2%
Bone Fracture	1	0.00%	0.2%
Allergy (Metal)	1	0.00%	0.2%

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

Safety of use of iFuse Implant System has been thoroughly evaluated.

A review of complaints during the first 5300 iFuse cases was reported by Miller et al. [Miller 2013[58]]. Event rates were low with a total complaint rate of 3.8%. The most commonly reported complaint was pain (2.2%) and nerve impingement (0.9%). 1.8% of patients underwent revision surgeries at a median of 4 months postoperatively.

The surgical revision rate after SIJF using iFuse Implant System was evaluated and reported in 2015. Based on combined information from the company's complaint database and sales information, the estimated 4-year surgical revision rate was <4% [Cher 2015[57]].

All adverse events in clinical trials were captured. Adverse events were defined broadly using the ISO 14155:2011 definition. The number of events specifically related to the implant or implant procedure was low. As summarized in a pooled analysis [Dengler 2017a[43]] of 326 patients undergoing SIJF with iFuse in 3 prospective trials:

- 4 (1.2%) underwent early surgical revision. In each case, one implant was inadvertently placed into the sacral foramen causing radicular pain. In each case, pain resolved after repositioning of the implant.
- 9 (2.8%) underwent late revision surgery, typically done to address pain and sometimes associated with poor implant position.
- 8 (2.5%) had wound-related issues. 1 subject required surgical washout. All other subjects were treated with medical therapy and local wound care. No subject had implant removal due to bone infection.

These are low event rates compared to other spine surgeries.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Two approaches to meta-analysis were done: 1) pooled analysis, and 2) systematic review with graphical analysis.

The first approach, an **individual patient-level meta-analysis**, combined data from three prospective trials (INSITE, iMIA, and SIFI). This approach is best as these trials were of the highest quality (prospective, performed under study protocols, monitored and source verified). Moreover, since data were available for all 3 studies, individual patient-level data were combined. This approach is far superior to standard meta-analysis, which combines data at the study level and cannot take into account individual potential confounders.

This analysis, published by Dengler et al [Dengler 2017a[43]], involved 423 patients in all 3 trials, including 326 who underwent SIJF and 97 who underwent NSM.

In the 3 pooled trials, mean (SD) age was 50.4 (11.2) years, most (70.4%) subjects were women, and pain duration averaged 5.5 years (6.7). Mean baseline SIJ pain (80 points, SD 12.5) and ODI scores (55 points, SD 12.7) were high. Quality of life was diminished (mean EQ-5D TTO of 0.43, mean SF-36 PCS of 31). Smoking was less common in US patients.

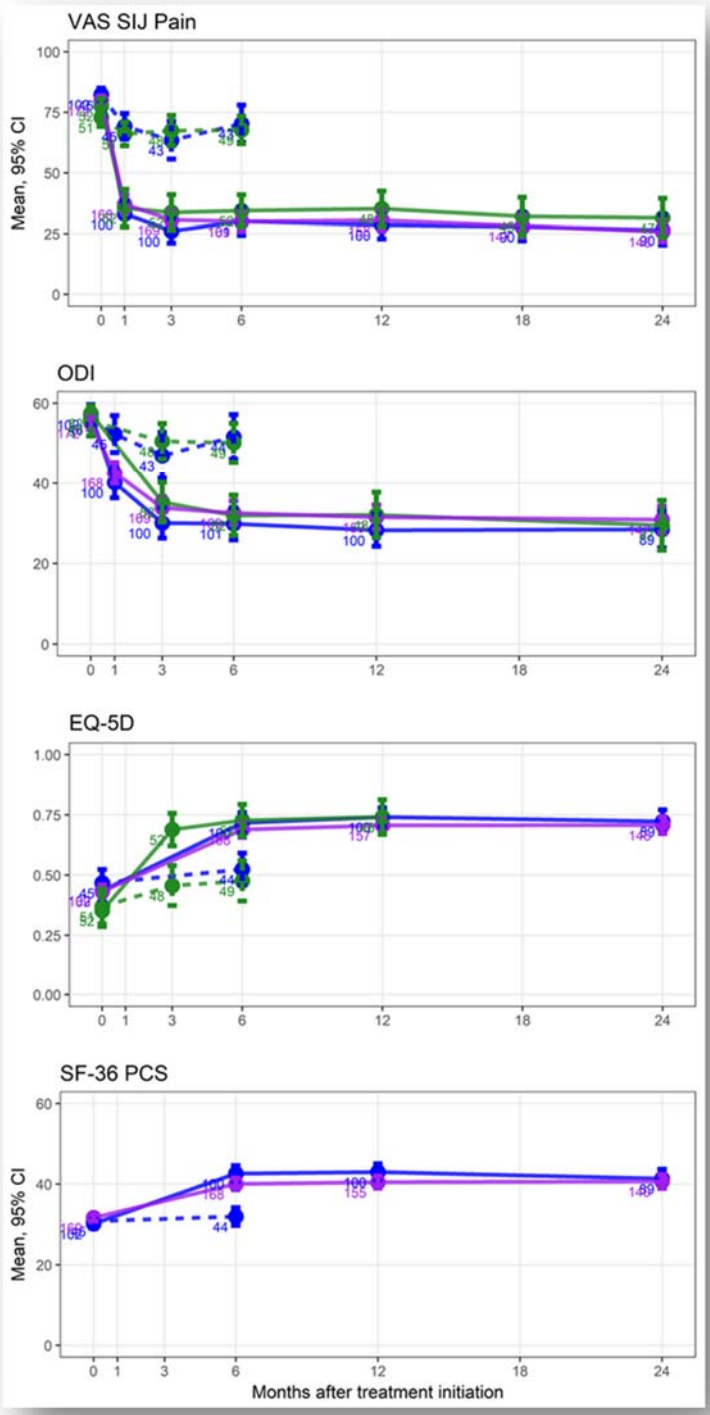
Operative characteristics were similar across groups. Operating time averaged 48 minutes and 3 implants were used in most cases.

Treatment effect estimates took into account all assessments prior to month 6 and used random effects models. The adjusted reduction in SIJ pain was 37.9 points larger (95% CI 32.5-43.4, p<.0001) in the SIJF groups vs. the NSM groups. Similarly, the improvement in ODI was 18.3 points larger (95% CI 14.3-22.4, p<.0001) and the improvement in EQ-5D TTO index was 0.24 points larger (95% CI 0.17-0.30, p<.0001). Extensive modelling was used to evaluate for effect modifiers (*i.e.*, interaction terms) but none were found.

Moreover, there was no evidence of heterogeneity of effects and effect sizes across studies.

Figure 11 – Pooled Analysis Results

Summary of pain, disability and quality of life scores in 3 prospective clinical trials. Blue = INSITE; green = iMIA and purple = SIFI. The plot shows marked homogeneity of responses across trials.



Subgroup analysis showed that two factors (non-use of opioids and non-smoking) predicted slightly larger improvements in pain and disability rating scores. However, in these two subgroups, outcomes (VAS SI Joint Pain and ODI) demonstrated improvements that were statistically significant and greater than the minimum clinically important difference (MCID) or substantial clinical benefit (SCB) for both measures. [MCID reference: Copay 2008[81]; SCB reference: Glassman 2008[82]].

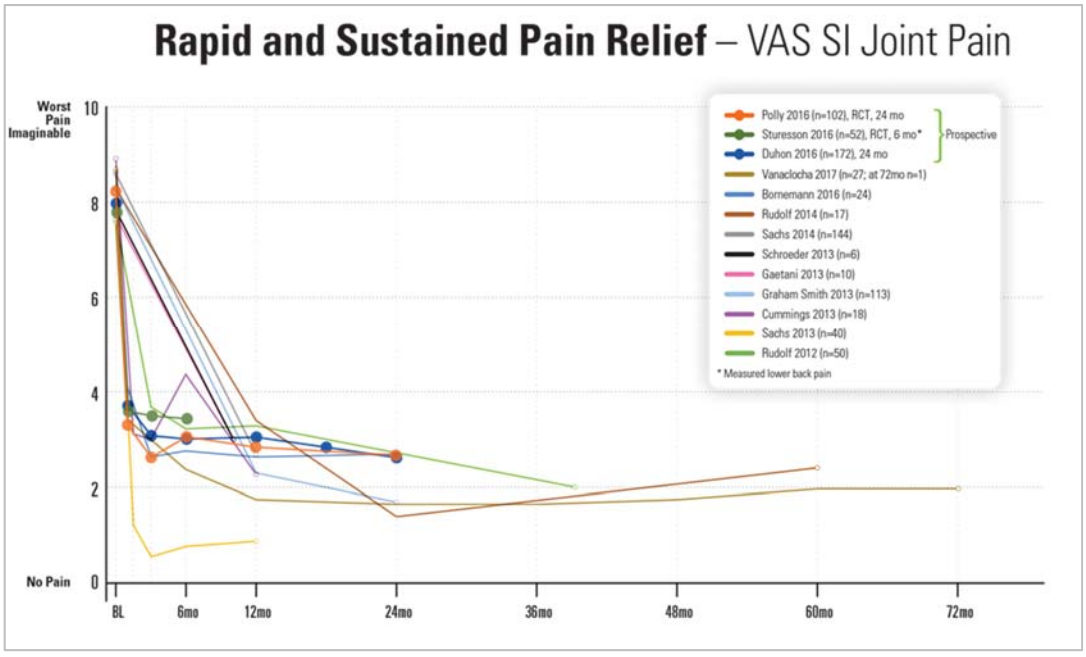
The 4 subgroups described in the initial scope of NICE MT355 were considered, and patient-level analysis showed no difference in outcomes or adverse events in these subgroups:

- women of reproductive age
- number of implants inserted
- unilateral versus bilateral SI joint implants
- previous lumbar surgery

Importantly, p-values comparing surgical and non-surgical treatments were very low, excluding chance as a potential cause of differences.

The second approach, **a systematic review with graphical analysis**, involved combine all known studies of SI joint fusion using the iFuse Implant System. This approach includes both prospective studies and retrospective studies, the latter typically reporting only pain levels. As shown below, all studies showed long-term improvements in SIJ pain.

Figure 12 – Combined Studies, VAS SI Joint Pain



7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

See response above.

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

Clinical studies of SIJ fusion using iFuse Implant System show the following:

- **Superior to Non-Surgical Treatment**
  - More improvement in SIJ pain after SIJF compared to non-surgical treatment
  - More improvement in disability (as measured by ODI) after SIJF compared to non-surgical treatment
  - More improvement in quality of life (as measured by EQ-5D and SF-36) after SIJF compared to non-surgical treatment
  - More improvement in physical function parameters (active straight leg raise test, number of positive physical examination signs, self-reported ability to walk) after SIJF compared to non-surgical treatment

  Pain Relief – clinically important, rapid (within 1 month) and sustained (12, 24, 40, and 60 month) decrease in VAS pain (~50 points on 0-100 scale)
  Back Function Improvement – clinical important reduction in disability as measured by ODI at 6, 12, and 24 months (~30-point reduction)
  Reduction in Opioid Use
  High Patient Satisfaction (> 90%)
  Low rates of device- or procedure-related adverse events
  Low rates of surgical revision
  Durable results – sustained outcomes to 3, 4, 5, and 6 years.

Of note, no other treatment for chronic SIJ pain has been shown to result in long-term improvement.

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The evidence base is strong, with two independent prospective randomized controlled trials in real-world settings, a second prospective multicentre trial with very similar results, and a number retrospective case series and comparative case series. The level of high-quality evidence supporting SIJ fusion is at least as high as other similar procedures. Many spine procedures are commonly performed but are not backed by randomized trials in the real-world setting that compare surgery vs. no surgery.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

For patients with disabling symptoms attributable to the SIJ who do not respond to non-surgical treatments, surgical management is a reasonable option. Minimally invasive surgical SIJ fusion with the iFuse Implant System is a proven technology with durable results.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The three prospective clinical trials were run in the real-world setting. In the EU trial, investigators' experience with the device was relatively low. Nonetheless, trial findings strongly supported device efficacy and safety. It is expected that device performance and health benefits in standard practice would therefore be similar to what was observed in the studies.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Criteria for patient selection are standardized. Those criteria used in clinical trials are identical to those used in standard clinical practice.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement (www.prisma-statement.org/statement.htm).

A PDF copy of all included studies should be provided by the sponsor.

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

PubMed search was performed on November 27, 2017 using the search terms "economic" AND "sacroiliac." Sorting by PubMed's "Best Match" algorithm, resulted in 45 publications. Review of titles resulted in 12 publications that specifically focused on the sacroiliac joint. Of these 12

publications, 5 specifically deal with analysis of minimally invasive SI joint fusion.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1: Selection criteria used for health economic studies

Inclusion criteria	
Population	PubMed.gov
Interventions	Terms “economic” AND “sacroiliac”; Filtered results for those specifically dealing with economic aspects of sacroiliac joint treatments.
Outcomes	
Study design	
Language restrictions	
Search dates	November 27, 2017
Exclusion criteria	
Population	
Interventions	None sacroiliac focused
Outcomes	
Study design	
Language restrictions	
Search dates	November 27, 2017

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The number of studies included and excluded at each stage is illustrated in the flow diagram in **Figure 13**3 below.

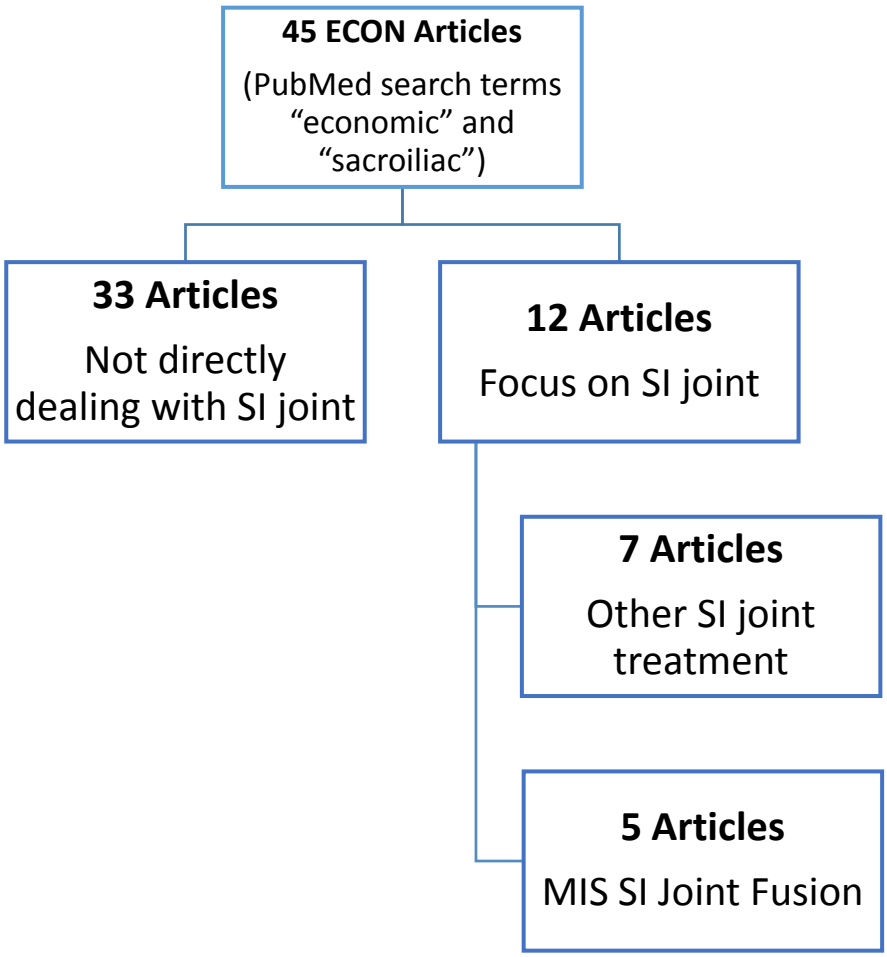


Figure 13 – Flow diagram of health economic articles identified in the systematic searches

8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

Outcome measures should be included if applicable. Patient outcomes could include gains in life expectancy, improved quality of life, longer time to recurrence, and comparative.

Table C2: Summary list of all evaluations involving costs

Study name (year)	Location of study	Summary of model and comparators	Patient population (key characteristics, average age)	Costs (intervention and comparator)	*Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)*	*Results (annual cost savings, annual savings per patient, incremental cost per QALY)*
Ackerman 2013 [76] Comparison of the costs of nonoperative care to minimally invasive surgery for sacroiliac joint disruption and degenerative sacroiliitis in a United States Medicare population: potential economic implications of a new minimally-invasive technology. ***Clinicoecon Outcomes Res. 2013 Nov 20;5:575-87. doi: 10.2147/CEOR.S52967. eCollection 2013.***	United States	Economic model comparing costs of treatment SI joint dysfunction patient with MIS SI joint fusion and non-operative care.	United States Medicare population with SI joint dysfunction (hospital inpatient setting)	MIS SI joint fusion vs. Non-operative care* Costs included treatment, follow-up, diagnostic testing, and retail pharmacy pain medication. *Cost of non-operative care were estimated from the 2005-2010 Medicare 5% Standard Analytic Files using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 720.2, 724.6, 739.4, 846.9, or 847.3.	Lifetime costs (cost per patient)	Extrapolated lifetime costs: $48,185/patient MIS SI joint fusion $51,543/patient non-operative care Resulting in a $660 million savings to Medicare over patients' lifetime.

Study name (year)	Location of study	Summary of model and comparators	Patient population (key characteristics, average age)	Costs (intervention and comparator)	*Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)*	*Results (annual cost savings, annual savings per patient, incremental cost per QALY)*
Ackerman 2014 [79] Comparison of the costs of nonoperative care to minimally invasive surgery for sacroiliac joint disruption and degenerative sacroiliitis in a United States commercial payer population: potential economic implications of a new minimally invasive technology. ***Clinicoecon Outcomes Res. 2014 May 24;6:283-96. doi: 10.2147/CEOR.S63757. eCollection 2014.***	United States	Economic model comparing costs of treatment SI joint dysfunction patient with MIS SI joint fusion and non-operative care.	United States Commercial payor population with SI joint dysfunction	MIS SI joint fusion* vs. Non-operative care** Costs included treatment, follow-up, diagnostic testing, and retail pharmacy pain medication. *MIS SI joint fusion costs were based on the Premier's Perspective Comparative Database and professional fees on May 2012 Medicare payment for CPT code 272780. **Non-operative care costs were from a retrospective study of Truven Health MarketScan data.	Cumulative 3-year (base-case analysis) and 5-year (sensitivity analysis) in commercial insurance payments (cost of nonoperative care minus cost of MIS SI joint fusion)	$14,545/patient (base-case) $6,137/patient (sensitivity analysis) Cost neutrality was achieved at 6 years. Higher initial procedural costs for the MIS SI joint fusion were largely offset by decreased nonoperative care costs over 5-year time horizon.

Study name (year)	Location of study	Summary of model and comparators	Patient population (key characteristics, average age)	Costs (intervention and comparator)	*Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)*	*Results (annual cost savings, annual savings per patient, incremental cost per QALY)*
Cher 2016 [83] Cost-effectiveness of minimally invasive sacroiliac joint fusion. ***Clinicoecon Outcomes Res. 2015 Dec 18;8:1-14. doi: 10.2147/CEOR.S94266. eCollection 2016.***	United States	Markov cost-utility model to evaluate 5-year health quality and costs after MIS SI joint fusion.	Data from 2 prospective, multicenter, clinical trials (INSITE and SIFI)	MIS SI joint fusion with iFuse Implant System	SIJ fusion was associated with a gain of approximately 0.74 quality-adjusted life years (QALYs) at a cost of US$13,313 per QALY gained.	Compared to traditional non-surgical treatments, MIS SI joint fusion is a cost-effective, and, in the long term, cost-saving strategy for the treatment of SIJ dysfunction.

Study name (year)	Location of study	Summary of model and comparators	Patient population (key characteristics, average age)	Costs (intervention and comparator)	*Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)*	*Results (annual cost savings, annual savings per patient, incremental cost per QALY)*
Saavoss 2016 [84] Productivity benefits of minimally invasive surgery in patients with chronic sacroiliac joint dysfunction. ***Clinicoecon Outcomes Res. 2016 Apr 11;8:77-85. doi: 10.2147/CEOR.S101607. eCollection 2016.***	United States	Regression model using data from National Health Interview Survey, and prospective individual patient data from INSITE.	Patients ages 21 to 70 with SI joint dysfunction that is a direct result of SI joint disruption and/or degenerative sacroiliitis, and who failed to achieve acceptable symptom relief after a minimum of 6 months of conservative care.	MIS SI joint fusion vs. Non-operative care	Worker productivity after treatment Expected change in earnings	Improved worker productivity when treated with MIS SI joint fusion. Patients who received MIS SI joint fusion (iFuse Implant) have an expected increase in the probability of working of 16% relative to non-surgically treated patients. The expected change in earnings across groups was US $3,128 (not statistically significant). Combining the two metrics, the annual increase in worker productivity given surgical vs nonsurgical care was $6,924 (95% CI $1,890–$11,945).

Study name (year)	Location of study	Summary of model and comparators	Patient population (key characteristics, average age)	Costs (intervention and comparator)	*Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)*	*Results (annual cost savings, annual savings per patient, incremental cost per QALY)*
Polly 2016 [28] Ignoring the Sacroiliac Joint in Chronic Low Back Pain is Costly ***Clinicoecon Outcomes Res. 2016 Jan 21;8:23-31.*** ***doi: 10.2147/CEOR.S97345. eCollection 2016.***	United States	Decision analytic model calculating 2-year direct health care costs in patients with chronic LBP considering lumbar fusion surgery	Patients with chronic LBP considering lumbar fusion surgery	Modeled two strategies: • one in which the SIJ is considered as a potential cause of low back pain and • one in which it is not.	Direct healthcare costs	Strategy of including the SIJ in the preoperative diagnostic workup of chronic low back pain saves an expected US$3,100 per patient over 2 years.

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table C3: Quality assessment of health economic studies

Study name: Ackerman 2013 – Medicare: cost of NSM vs MIS SI Joint Fusion[76]		
Study design	Comparative Cumulative Cost Model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	Economic cost of SI joint dysfunction treatment.
2. Was the economic importance of the research question stated?	Yes	LBP is a known economic burden. SI joint dysfunction is a known cause of LBP, but there have been very few economic/cost publications.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	All assumptions and methods were detailed.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Non-surgical management is the current standard of care for SI joint dysfunction.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Table 1
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	-NA-	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	-NA-	In most cases, only a small number of non-combinable studies available
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	-NA-	No health state utility analysis was performed

13. Were the details of the subjects from whom valuations were obtained given?	-NA-	
14. Were productivity changes (if included) reported separately?	-NA-	
15. Was the relevance of productivity changes to the study question discussed?	-NA-	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	All in $USD
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Lifetime cost savings reported in 2012 US dollars
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Cumulative cost model with relevant time horizon
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	Discount rates may change depending on perspective
25. Was an explanation given if cost or benefits were not discounted?	-NA-	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No statistical testing performed
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Relevant comparator is non-surgical care
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: **Ackerman 2014 – Commercial Payor: cost of NSM vs. MIS SI Joint Fusion**[79]		
Study design	Comparative Cumulative Cost Model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To compare the cost of treating SI joint dysfunction with NSM vs. MIS SI Joint Fusion in the commercial payor population.
2. Was the economic importance of the research question stated?	Yes	LBP is a known economic burden. SI joint dysfunction is a known cause of LBP, but there have been very few economic/cost publications.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	All assumptions and methods were detailed.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Non-surgical management (NSM) is the current standard of care for SI joint dysfunction. MIS SI joint fusion has shown to provide clinically significant improvement in patients' pain, disability, and quality of life.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Comparing costs of treatment: • Cumulative 3-year costs (base-case analysis) • 5-year differentials (sensitivity analysis)
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	The goal was to compare cumulative treatment costs of one treatment vs. the other
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	-NA-	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Nonoperative care costs (diagnostic testing, treatment, follow-up, and retail pharmacy pain medication) were from a retrospective study of Truven Health MarketScan® data. MIS fusion costs were based on the Premier's Perspective™ Comparative Database and professional fees on 2012 Medicare payment for Current Procedural Terminology code 27280.

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	-NA-	Article focused on costs only
13. Were the details of the subjects from whom valuations were obtained given?	-NA-	Article focused on costs only
14. Were productivity changes (if included) reported separately?	-NA-	Article focused on costs only
15. Was the relevance of productivity changes to the study question discussed?	-NA-	Article focused on costs only
16. Were quantities of resources reported separately from their unit cost?	-NA-	
17. Were the methods for the estimation of quantities and unit costs described?	-NA-	
18. Were currency and price data recorded?	Yes	Costs in $USD
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Lifetime cost savings reported in 2012 US dollars
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Tables 1 & 2 provide all assumptions to generate the economic model
22. Was the time horizon of cost and benefits stated?	Yes	3- and 5-year horizons reported
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	3% is a standard rate. Discount rates can vary widely given the reader's perspective.
25. Was an explanation given if cost or benefits were not discounted?	-NA-	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	Not done

27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Cher 2014 – Cost-effectiveness of MIS SI Joint Fusion (iFuse)[83]		
Study design	Markov cost-utility model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To determine the cost-effectiveness of MIS SI joint fusion.
2. Was the economic importance of the research question stated?	Yes	Cost-effectiveness of MIS SI joint fusion had not been reported.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	MIS SI joint fusion was compared to traditional non-surgical treatment
5. Were the alternatives being compared clearly described?	Yes	Data was from 2 prospective, multi-centre, clinical trials, one a single-arm trial (SIFI) and the other a randomized controlled trial (INSITE).
6. Was the form of economic evaluation stated?	Yes	Standard cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Further details available in other study publications
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	-NA-	Most estimates from a single study. Some estimates taken from a single sister study (SIFI). Meta-analysis not relevant
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Markov model used to approximate quality-adjusted life years (QALYs) at a cost, which in turn is used to determine the incremental cost-effectiveness (ICER) ratio.
12. Were the methods used to value health states and other benefits stated?	Yes	Based on QOL measures from within trial

13. Were the details of the subjects from whom valuations were obtained given?	Yes	No direct valuations obtained. Rather estimates derived from in-trial QOL surveys
14. Were productivity changes (if included) reported separately?	-NA-	Article focused on direct costs and health utility only
15. Was the relevance of productivity changes to the study question discussed?	-NA-	Article focused on direct costs and health utility only
16. Were quantities of resources reported separately from their unit cost?	Yes	Due to space limitations not all values reported
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	All in USD
19. Were details of price adjustments for inflation or currency conversion given?	-NA-	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	-NA-	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	See Figure 1 – Overview of structure for the decision analysis model
28. Was the choice of variables for sensitivity analysis justified?	Yes	All variables were subject to sensitivity analysis
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	The relevant comparator is non-surgical treatment
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Saavoss 2016 – Productivity after MIS SI Joint Fusion (iFuse)[84]		
Study design	Regression Model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	Impact of MIS SI joint fusion on worker productivity
2. Was the economic importance of the research question stated?	Yes	Impact of MIS SI joint fusion on worker productivity is not known
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Compared to nonsurgical management the current standard of care
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Calculation of expected changes in productivity and related costs
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	The study used data from two sister prospective clinical trials (meta-analysis not done for just 2 trials).
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	-NA-	
13. Were the details of the subjects from whom valuations were obtained given?	-NA-	

14. Were productivity changes (if included) reported separately?	Yes	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	Not used
24. Was the choice of rate justified?	-NA-	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Time horizon for analysis was relatively short. Discounting not relevant
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	No	Not done in this study
28. Was the choice of variables for sensitivity analysis justified?	-NA-	
29. Were the ranges over which the parameters were varied stated?	-NA-	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Relevant comparator is non-surgical care
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Polly 2016 – Ignoring the SI Joint is Costly (iFuse)[28]		
Study design	Decision Analysis	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To determine impact of failure to consider the SIJ on cost of pre-surgical low back pain patients
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Yes. Relevant comparator is lumbar spine fusion surgery
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Summarized in this article. Further details available in other study publications
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	-NA-	Most effectiveness estimates taken from two very similar prospective trials (including 1 RCT). Meta-analysis not relevant
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	-NA-	No health state utility calculations

13. Were the details of the subjects from whom valuations were obtained given?	-NA-	
14. Were productivity changes (if included) reported separately?	-NA-	Article focused on direct costs only
15. Was the relevance of productivity changes to the study question discussed?	-NA-	Article focused on direct costs only
16. Were quantities of resources reported separately from their unit cost?	Yes	Generally only 1 resource per unit used
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	All in USD
19. Were details of price adjustments for inflation or currency conversion given?	-NA-	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	No discounting used given short-time frame (2 years)
24. Was the choice of rate justified?	-NA-	
25. Was an explanation given if cost or benefits were not discounted?	-NA-	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	The relevant comparator surgical treatment of the lumbar spine, which, in many cases, might be a misdiagnosis
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Only 1 outcome (direct cost) subject to several types of sensitivity analysis
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

A de novo analysis was developed to estimate the cost and consequences of using the iFuse Implant System from an NHS payer perspective compared to:

- open sacroiliac joint fusion surgery using screw or cage systems;
- non-surgical or conservative management;
- repeat steroid injections.

Section 8 reports that 5 economic evaluations have considered the cost-effectiveness of the iFuse Implant System. However, none of these studies address the decision question, comparing the iFuse Implant System to all relevant comparators from an NHS payer perspective.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

The patient group considered in this analysis is patients diagnosed with chronic SIJ pain who have been unsuccessfully treated with conservative management and continue to live with chronic pain.

Subgroups such as women of reproductive age and patients with previous lumbar surgery were not considered separately. This is because clinical

outcomes (success rates) and resource use (procedure time, length of stay and revision rates) were not expected to differ across these groups.

Unilateral versus bilateral sacroiliac joint implants were also not considered separately in the cost analysis comparing iFuse Implant System with open surgery. Feedback from internal and external experts suggest that bilateral procedures were almost always conducted as two separate surgical procedures for safety reasons, irrespective of whether surgery was performed with the iFuse Implant System or using an open surgical approach. The costs of bilateral procedures are therefore equivalent to two unilateral procedures.

The number of iFuse surgical implants was also not considered in subgroup analysis as most surgeries with the iFuse Implant System require 3 implants. Any variation outside of this was captured in the sensitivity analysis.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

The comparators used in the cost analysis are aligned with those listed in the scope. A description of each comparator is described below to provide context to the resource use assumptions applied in the cost analysis.

Open Surgery

Open sacroiliac joint fusion surgery using screw or cage systems, hereby referred to as 'open surgery', is the primary comparator in this analysis. This is because open surgery is the only curative treatment offered to patients who have progressed through conservative management treatments and continue to live with chronic SIJ pain. Uptake of open surgery for chronic SI joint pain has historically been low as these are very invasive procedures associated with considerable side effects. Several techniques for open fusion of the SI joint have been reported which vary in terms of the surgical approach and the consumables used. These are typically categorised as being either an anterior or posterior open surgical procedure.

Posterior open surgical procedures require more surgical consumables compared to using an anterior approach, however anterior procedures are associated with longer procedure times. Examples of anterior and posterior open surgical techniques described in clinical papers are provided in Appendix A. These studies were used to inform the resource use assumptions applied in the cost analysis.

In the base case cost analysis, a 50:50 split between anterior and posterior procedures is assumed as this approach captures the variation in resource use (consumables, procedure times and length of stay) and total costs. This split is varied to consider 100% of open surgeries being posterior or anterior respectively in the deterministic sensitivity analysis. Similarly, the probabilistic sensitivity analysis draws from a beta distribution ranging between 0%-100%.

Stepped pathway

As detailed in the MTEP scope, minimally invasive surgery (MIS) with the iFuse Implant System is intended to be offered after standard conservative management treatments have proven unsuccessful. First-line treatment of patients with chronic SI joint pain is expected to be as follows:

- referral to a pain management clinic;
- steroid injection, to confirm diagnosis of SIJ pain and provide immediate relief;
- referral to a course of physical therapy (feedback provided by clinicians suggests that patients are typically offered 6 to 12 sessions);
- prescription of pain medication, typically starting with a low dose opioid regimen

While the evidence on the effectiveness of physical therapy along with other conservative management treatments is limited, it is assumed that some patients will have sufficient relief at this stage to be discharged from the pain clinic and will not require any further treatment. Prior economic evaluations of conservative management suggest that approximately 27% of patients have an improvement in their pain score (moving from severe to mild/moderate) after initial treatment with conservative treatment.[83]

This analysis considers the costs and outcomes amongst patients that continue to live with severe chronic SI joint pain after unsuccessful initial conservative management. This is intended to inform the decision regarding the point at which patients should be offered MIS with the iFuse Implant System.

Consultation with pain management consultants suggest that management of patients that continue to report severe chronic SI joint pain after initial conservative treatments is variable and likely to include a combination of following:[85]

- **Some patients may be offered repeat steroid injections**. Magnetic resonance imaging (MRI) guided steroid injections to the SI joint temporarily numb chronic pain. Repeat injections are therefore required for long-term chronic pain management. Steroid injections are not recommended by NICE due to limited evidence on their efficacy.[85] In most cases the numbing effect of injection wears off within 2-4 weeks. Feedback from clinicians suggest that some patients report pain relief with steroid injections that lasts up to 3-4 months. These patients may be offered 2 to 3 injections per year, however funding for repeat steroid injection varies regionally due to lack of supporting clinical evidence. Amongst patients treated with repeat steroid injections, it is common for patients to stop coming back for treatment as benefits decline or funding is denied.

- **Some patients may move to radiofrequency (RF) ablation or a denervation procedure.** RF ablation injection procedures are delivered via an x-ray guided needle, under anaesthetic or mild sedation. These procedures also temporarily numb chronic pain, therefore repeat procedures may be required. While RF ablation procedures are recommended by NICE, the evidence supporting efficacy of RF ablation is limited to two short-term clinical trials that have demonstrated more pain relief than sham.[86,87] RF ablation is not demonstrated to provide long-term pain relief and the procedure typically needs to be repeated every 2-3 years.

- Patients not treated with repeat steroid injections or RF ablation are expected to live with severe chronic pain, managed by pain medication. These patients are expected to regularly attend their GP or a pain management clinic to be assessed and prescribed an opioid-based drug regimen. Opioid regimens vary widely in costs, ranging from high cost branded analgesics to generic compound analgesic of codeine and paracetamol. Patients are typically started on a mild / moderate dose which will be reviewed and escalated if patients report continued pain or side effects. The BMA report a year on year increase in opioid prescribing in the community from 228 million items in 1992 to 1.6 billion in 2009.[88]

While opioid based regimens are expected to be widely used to treat all types of severe chronic back pain, including SIJ pain, there is a lack of consistent evidence of the long-term (beyond 12 weeks) benefits. Furthermore, long-term use of opioids is associated with a multitude of adverse events including nausea, headache, somnolence, urinary complications and constipation. Living with chronic pain also has a detrimental impact on patients' quality of life. 49% of people in the UK diagnosed with chronic pain suffer from

depression and chronic pain is associated with a wide range of negative health and social outcome including poor anxiety, job/income loss, impaired function and limited daily physical and social activities.[88]

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

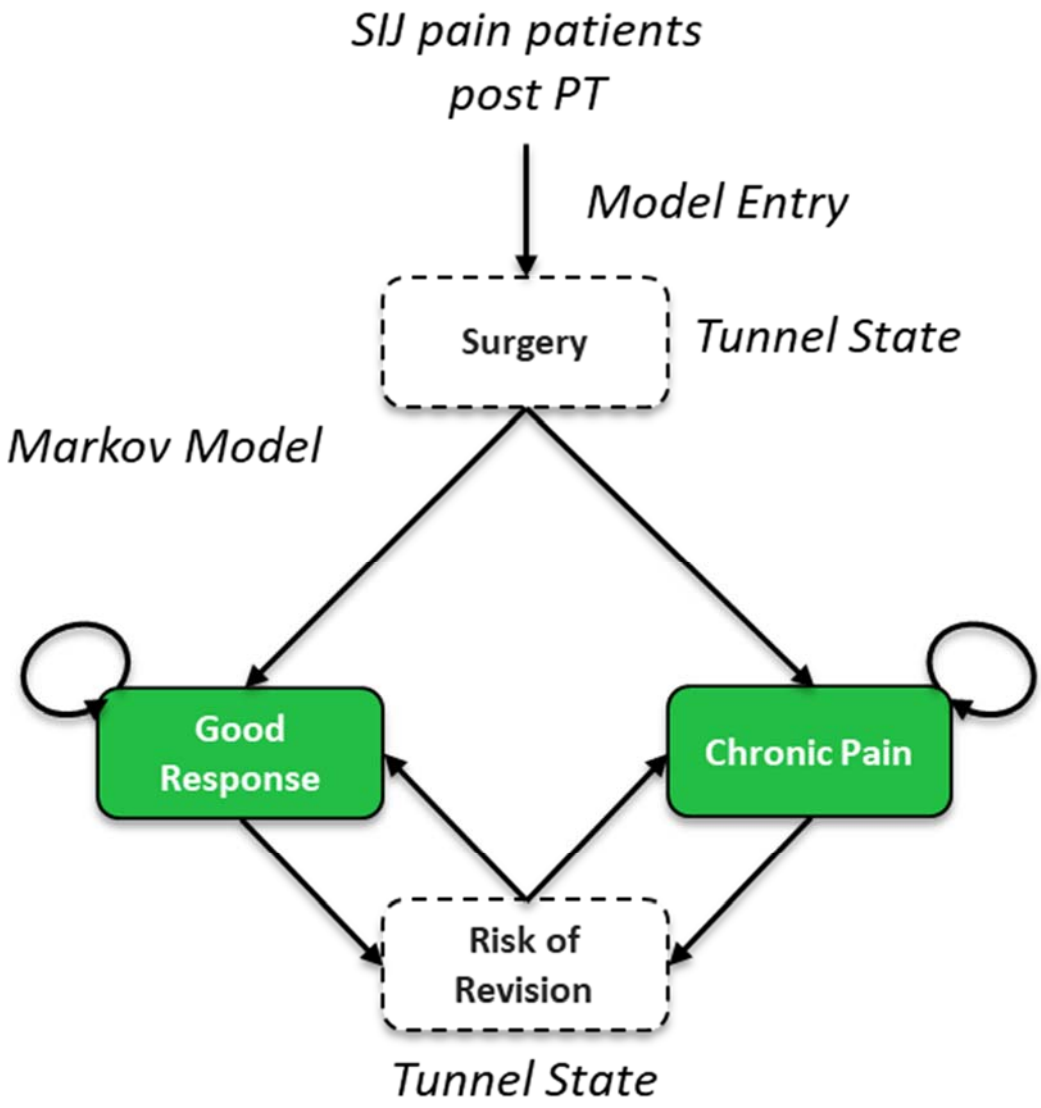


Figure 14 – Surgical treatment model structure

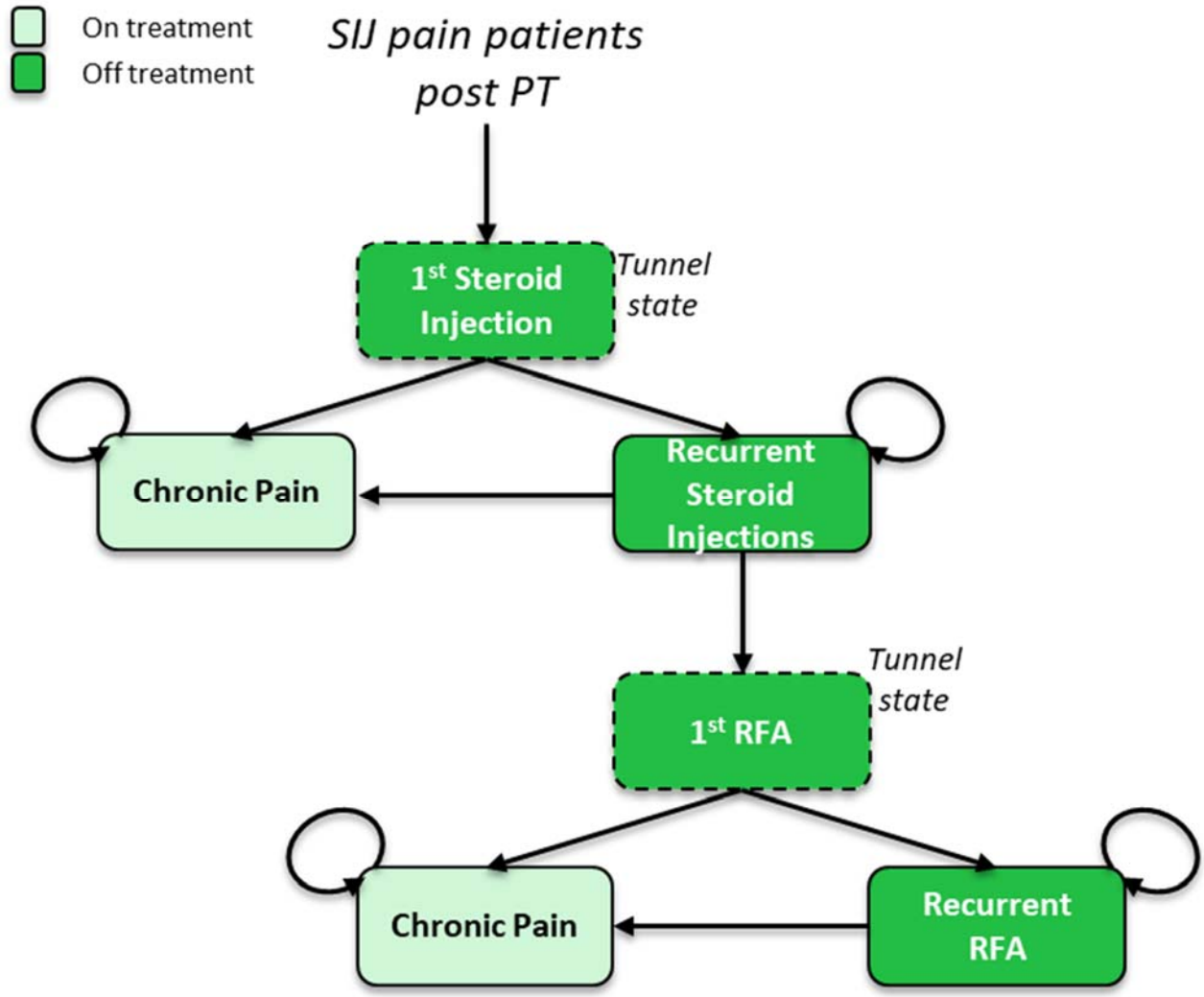
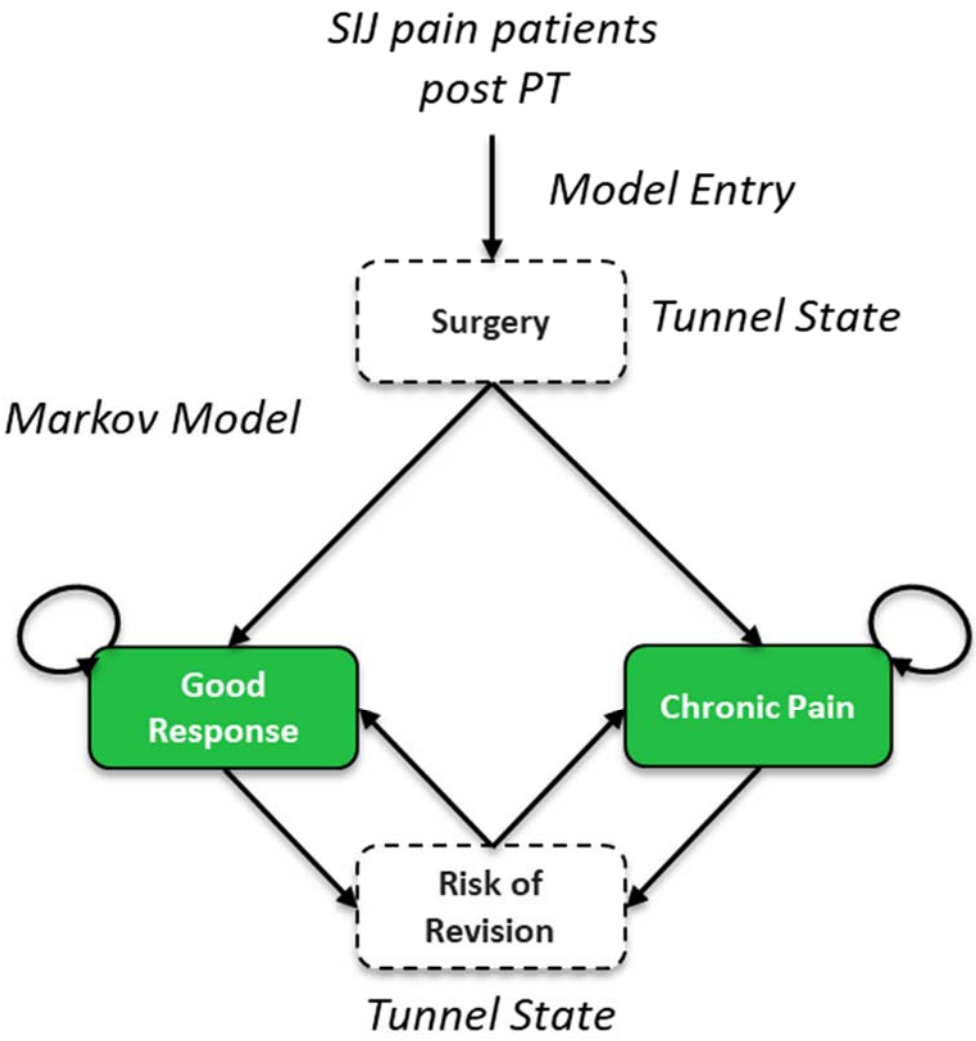


Figure 15 – Stepped pathway model structure

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

There are two model structures, a surgical treatment model and a stepped pathway treatment model, used to compare the treatment options as described in the response to question 3.3

(1) Surgical Treatment Model:



The surgical treatment model is a simple structure (

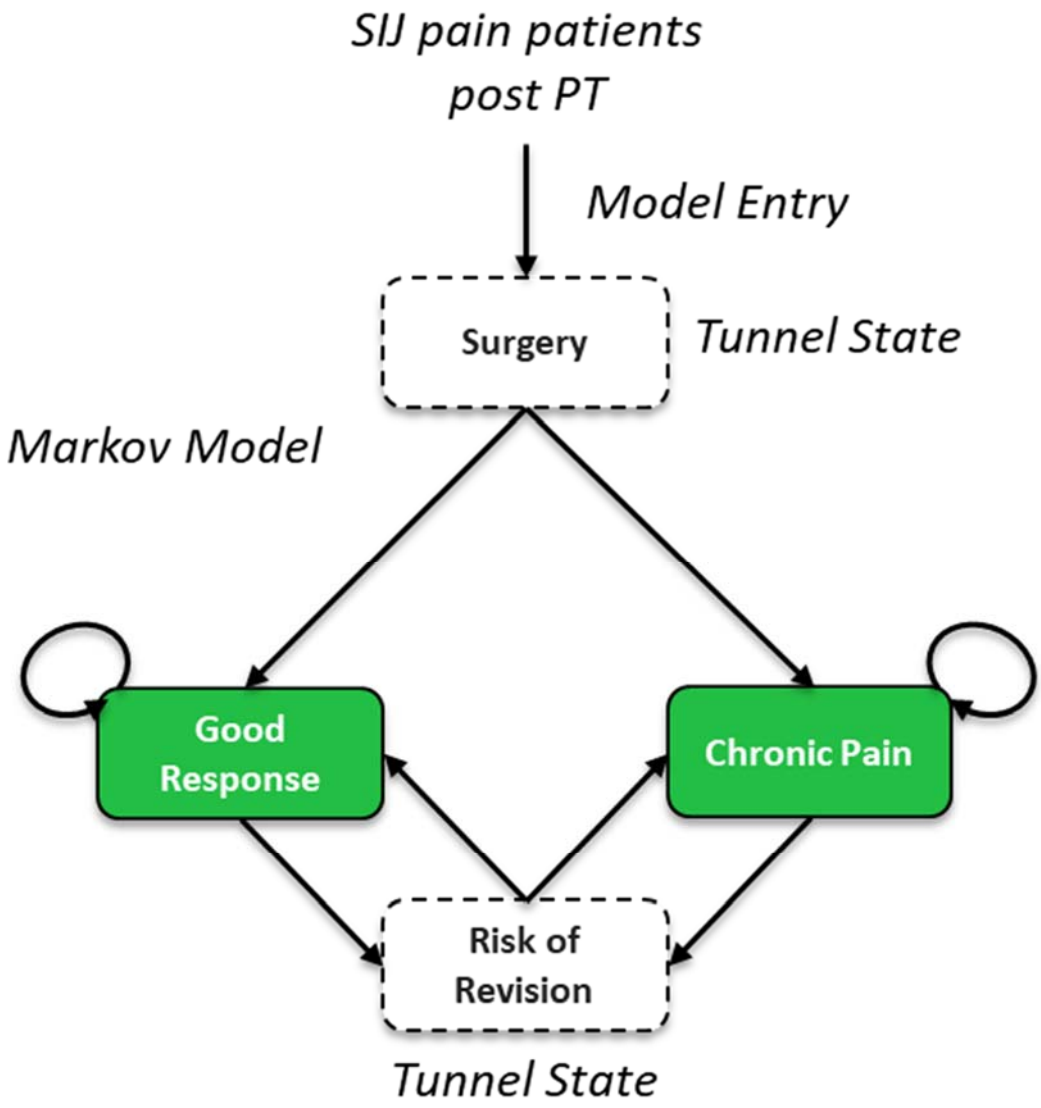


Figure 14) that reflects the like for like comparison between two alternative surgical options. The factors that are expected to influence resource use include procedure costs, recovery time, and revision rates.

This model is structured as a four state Markov model into which patients enter the 1st tunnel state, surgery, and then move to either a poor response, or a good response. From these two states they may either remain in the same state, or receive revision surgery via a revision tunnel state.

(2) Stepped Pathway Model:

The stepped pathway model is a more complex structure (*Figure 15*) as it incorporates movement through a stepped pathway. This enables the model to capture how costs differ depending on how long patients stay on each

treatment, the proportion that progress to more invasive treatments and the proportion that stop all treatments over time.

The stepped pathway is a 6 state Markov model that reflects the use of repeated steroid injections, repeated RF ablation procedures and living with chronic pain, managed by pain medication.

A decision was made not to incorporate physiotherapy into this structure as this would likely be offered prior to any of the treatment options listed and is not therefore a comparative option.

All patients enter the model into a tunnel state representing the 1st steroid injection a patient receives. Patients may then transition to a chronic pain state or a repeat steroid injection state depending on the response to the steroid injection. Over time patients may discontinue repeat steroid injections due to the transitory relief that a steroid injection provides.

Patients may also transition to receive RF ablation procedures which are represented by a tunnel state for the 1st procedure and a separate state for recurrent procedures. From both RF ablation and steroid injection states patients may transition to a chronic pain state. In this state they are assumed to be treated with an opioid pain management regimen.

iFuse Impant System versus Repeat Steroid Injections

The stepped pathway model (*Figure 15*) is also programmed to examine the cost difference between MIS with the iFuse Implant System and repeat steroid injections. In this case, the cost of repeat steroid injections is accumulated and discounted over time, but no transitions to other health states are allowed. This scenario aims to identify the point at which it is cost neutral to have treated patients with the iFuse Implant System instead of continued repeat steroid injections.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Table C4: List of assumptions in cost model

Aspect	Assumption	Rationale
Open surgery approach	50% of open surgeries use an anterior approach, the remainder use a posterior approach	Procedure times, length of stay and the consumables used are expected to vary across open surgical procedures. Assuming a 50:50 split between anterior and posterior and varying this assumption to consider 0-100% anterior in the sensitivity analysis is expected to capture this variability in costs.

Surgery response	Patients with a good response post-surgery remain in this health state for the duration of the model unless they have a revision surgery.	The proportion of patients with a good response post MIS with the iFuse Implant System at 2 years was very similar to at 3 years (84% compared to 83%) as detailed in the LOIS study reported in Section B 7.4.1. This suggests that outcomes reported at 2 years are likely to be sustained over the medium to long term.
	50% of patients who have a surgical revision will move into a chronic pain health state and the remainder will have a good response. This assumption was applied to both the iFuse Implant System and open surgery.	This assumption was applied as data was not available on the health outcomes post-surgical revision. This assumption reflects feedback from clinical experts that outcomes following a surgical revision are likely to be worse than first procedures. This assumption may favour the comparator where surgical outcomes are consistently reported to be worse with open surgery compared to the iFuse Implant System however the impact of this is expected to be minimal as revision surgeries following MIS with the iFuse Implant System are rare
Surgery revisions costs	The cost of revision surgery is assumed to be the same as the original surgical procedure minus the training costs and the cost of early revision.	This assumption was applied as no data was available for the procedure times and length of stay with revision surgeries. Clinical experts reported that revision surgeries are likely to be more expensive due to longer procedure times which are required because of the need to remove old consumables and implant new ones. Similarly, recovery times are likely to be longer following revision surgery as there is a higher risk of adverse events. The assumption to apply equal costs for initial and revision surgery is expected to favour the comparator as the revision rates with open surgery are considerably higher compared to the iFuse Implant System.
Pain medication	Patients living with chronic pain are treated with an opioid base regimen. 50% of patients are on a daily regimen = co-codamol 4 x 8/500 mg + naproxen 2 x 500 mg + Omeprazole 20 mg The other 50% are on a daily regimen = tapentadol 2 x 200 mg + naproxen 2 x 500 mg + Omeprazole 20 mg	Prescriptions for opioid based regimens are expected to vary widely. This is reflected in the wide number and type of opioid drugs used by patients as baseline, recruited to the iMIA trial (unpublished data). To capture this uncertainty, high- and low-cost scenarios were considered. The high cost scenario was based on a prescription provided by a UK patient diagnosed with chronic SIJ pain which included a branded slow release weak moderate strength opioid. In contrast, the low-cost scenario included a generic blend of a weak opioid, codeine, with paracetamol.

		A 50:50 split between the low and high cost scenario was applied to capture the wide variation in costs within the sensitivity analysis.
	All patients suffering with chronic pain will see their GP once every six months to obtain a repeat prescription for their pain medication regimen. In addition, patients on strong slow release opioids will also attend an outpatient visit with a pain management consultant every six-months to review their medication regimen.	The BMA (9) report "*Referral to specialist pain services is indicated where pain is associated with either or both high levels of distress and disability or when severe pain remains refractory to treatment*". However, the same report notes that access to pain management services is variable regionally. The assumption applied in the analysis reflects this variability as it assumes that half of those treated with opioid for chronic pain will be managed by a pain consultant and the remainder will only be seen by their GP.
Stepped pathway	Patients being treated with repeat steroid injections will not be in chronic pain while in this repeat steroid injection health state as treatment provides temporary pain relief	This assumption is based on the rationale that patients would only receive a repeat injection if they reported sustained pain relief for at least 3-4 months after their prior steroid injection. The assumption that pain relief lasts for a full 6-month cycle is conservative and expected to favour the comparator as in reality patients' pain levels are expected to increase over the course of the interval between injections as the effect of the injection wears off.
	Patients being treated with repeat steroid injections will not be on an opioid pain management regimen	This assumption is based on the rationale that injections provide temporary pain relief therefore further medication is not necessary. This assumption is conservative and expected to favour the comparator as it is likely that some patients may also be prescribed an opioid based regimen while on repeated steroid injections.

9.1.7 Define what the model's health states are intended to capture.

The model is designed to capture significant difference in resource use associated within each treatment arm. As such the health states differ by treatment arm as detailed below:

Surgical Treatment	
Surgery – iFuse	Captures the costs associated with surgery and immediate follow-up to 6 months. This includes revision surgery in the first 6 months.
Surgery – Open	Captures the costs associated with surgery and immediate follow-up to 6 months. This includes revision surgery in the first 6 months
Good response to surgery	Patients that have a good response to completed surgery move into a mild pain health state. Here they are not expected to incur any costs for pain medication or have regular visits with their physician other than scheduled follow up.
Poor response to surgery	Patients that have a poor response to completed surgery move to a chronic pain health state and are assumed to use an opioid based pain medication regimen and have regular visits with their physician or a pain management consultant
Revision Surgery	Patients that undergo revision surgery after 6 months are expected to incur the cost of a repeat surgical intervention. This cost is assumed to be the same as the initial surgery minus the cost of training and the cost of early revisions.
Stepped Pathway	
Steroid Injections (1st and recurrent)	Captures the average cost of steroid injections for a 6-month period. In this health state patients are assumed to have temporary relief from pain and a repeat injection after 3-4 months is required.
RF Ablation (1st and recurrent)	Captures the average cost of RF ablation injections for a 6-month period. This cost assumes a patient attends hospital for an RF ablation procedure. In this health state patients are assumed to have temporary relief from pain and require a repeat procedure after 1-2 years
Chronic Pain	Patients live with severe chronic pain managed with an opioid medication regimen. 50% of patients use moderately strong, slow release opioids and attend an outpatient visit with a pain management consultant every six-months. The other 50% are on a milder opioid based regimen. All patients attend a GP appointment every 6 months to fill their prescription.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C5: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	7 years	There is limited data on long term outcomes beyond 7 years	Assumption
Discount of 3.5% for costs	A discount rate of 3.5% is applied to all costs beyond 1 year.	Recommended by NICE technology evaluation programme	NICE 2012 [89]
Perspective (NHS/PSS)	UK NHS perspective	Recommended by NICE technology evaluation programme	NICE 2012 [89]
Cycle length	6-month time steps	Aligned with time points after which patients on the stepped pathway are likely to be reviewed and may change or stop treatment	Assumption
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Specific searches were not carried out to source clinical inputs, instead all clinical inputs were selected by Si-Bone in consultation with internal and external clinical experts. The sources selected included a combination of meta analyses and randomised controlled trials (RCTs) identified in the systematic literature reviews (SLRs) conducted alongside this analysis described in Section A, as well as feedback collected from interviews with clinical experts.

A description of the sources applied to calculate the clinical inputs and transition probabilities and the rationale for selecting these sources are described below.

Transition Probabilities - Response to treatment

The response to treatment transition probabilities refer to the proportion of patients that move to a mild/moderate pain condition after a surgical treatment. These data were sourced from Zaidi et al.[55] for both the iFuse Implant System and open surgery. This source was selected as this is a meta-analysis which reported satisfaction rates of MIS Fusion (which was based on the iFuse implant system) and open surgery and this source synthesised data

from 5 consecutive case series, 8 retrospective studies, and 3 prospective cohort studies.

The outcome applied was the mean probability of excellent patient satisfaction determined by pain reduction, function, and quality of life. As the outcome of the surgery occurs in the first six months and this is not expected to change over time no adjustment to the data was required to calculate the probability of this event in the model.

Transition probabilities - Response to treatment after surgical revision

The transition probabilities for 'response to treatment after surgical revision' refers to the proportion of patients that move to a mild/moderate pain condition after a surgical treatment. As limited data is reported in the literature on patients' pain levels after revision surgery this input was based on an assumption.

50% of patients are assumed to have a good response as outcomes with a revision surgery are expected to be lower post-revision surgery compared to first procedures. This assumption was applied to both the iFuse Implant System and open surgery and is aligned with the transition probabilities applied in the economic analysis by Cher et al.[83] This assumption is likely to favour the comparator as surgical outcomes are worse with open surgery compared to the iFuse Implant System. However, as surgical revisions with the iFuse Implant System are rare the impact of this is expected to be small.

Transition Probabilities - Surgical revisions

The transition probability for the proportion of patients likely to have a surgical revision after the iFuse Implant System at any time point were sourced for data on file collected by SI-BONE on 4-year survivorship analysis (free from revision surgery) estimated from inventory (> 11,000 US cases) and complaints databases managed by SI-BONE.[83] The cumulative rate of 3.4% was converted to biannual probability, assuming a uniform distribution of revisions over the 4-year period.

The transition probability for the proportion of patients likely to have a surgical revision with both types of open surgery was obtained from Zaidi et al.[55] This source was selected to be consistent with the source applied for the surgical outcomes. The mean reoperation rate was 15% over 5 years which was converted to a biannual probability, also assuming revisions were uniformly distributed over this period.

Transition Probabilities - Response to treatment in stepped pathway

The transition probability 'good response to treatment' in the steroid injection and RF ablation health states refers to the proportion of patients that remain in this health state and receive a repeat injection in the following time cycle.

As there was limited data on the efficacy of these treatments these probabilities were informed by expert opinion. Two pain management clinicians were consulted and a mid-point between was applied.

- For steroid injections, one clinician estimated 60%-70% of patients benefit and have a repeat injection, a second clinician estimated between 40-50% benefit and have repeat injections.
- For RF ablation, one clinician estimated 25%-30% of patients benefit and have a repeat procedure, a second clinician estimated 15% benefited from RF ablation but was very unsure as they rarely offered this.

As there was a lot of uncertainty around these data, wide confidence intervals were applied to account for this uncertainty in the sensitivity analysis.

Transition Probabilities - Discontinuation rates in stepped pathway

The discontinuation transition probabilities refer to the proportion of patients that stop repeat steroid injection or RF ablation or move from steroid injections to RF ablation procedures at any time point. Patients may stop treatment either because they are no longer benefitting, or treatment is no longer funded. These transition probabilities were sourced from expert opinion as these data are not reported in the literature.

These transition probabilities were sourced from an estimate provided by one clinician that reported the proportion of patients they would expect to have stopped treatment after 2 years. The biannual transition probabilities were calculated assuming:

- 15% of those on steroids would discontinue all treatments between 6 months and 2 years
- 25% of those on steroids would move to RF ablation by 2 years
- 75% of those on RF ablation would discontinue all treatments by 2 years.

Resource use inputs – Procedure Time & Length of Stay

Procedure times with the iFuse Implant System were obtained from Heiney et al.,[54] which is a systematic review and meta-analysis that aimed to summarize

operative measures and clinical outcomes reported in published studies of MIS SI joint fusion. A meta-analysis was selected as this included a larger population and captured variation across individual studies. The meta-analysis used to source the transition probabilities for success rates[55] could not be used as this study did not report resource utilisation data.

Procedures times for open surgery were sourced from individual studies as Heiney et al.[54] did not report the results separately for conducting procedures using an anterior or posterior approach and these were expected to differ.

2 studies were identified that described resource utilisation for posterior fusion of the SIJ.[44,90] Only one of these[44] reported procedures times and length of stay which was used to source this input.

7 studies[46,91–96] were identified that described resource utilisation for anterior fusion of the SIJ. Two of these[46,96] reported procedures and length of stay. The point estimates for procedure time and length of stay were sourced from Nyström et al.[96] as this was a larger and more recent study. The range around the point estimates was adjusted to incorporate the wider range reported in Ledonio et al.[46]

To validate the inputs for the procedure times and length of stay the inputs sourced from the literature were compared with the average procedure times reported by two UK surgeons with experience performing MIS with the iFuse Impant System. The surgeon's estimates for procedures times with the iFuse Implant System were similar but lower than times reported in the meta-analysis. One surgeon reported under an hour and the second surgeon reported 45 minutes, compared to a point estimate of 59 minutes reported in Heiney et al.[54] The second surgeon noted that procedure times are influenced by the teams' experience, particularly the skill and experience of the radiographer and noted that their procedure times have decreased over time. When he works with his most experienced radiographer he can now perform procedures in 30 minutes, with a lower range of 20 minutes. This suggests that the procedure times reported in clinical trials may be longer than in the real world due to a learning curve as surgical teams become more familiar with the procedure.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

In the surgical treatment arm all patients were assumed to remain in the same health state (good response or chronic pain) unless they had a surgical revision. This assumption is consistent with 3-year outcomes reported for iFuse, as reported in section 5, on-going studies. Follow-up from LOIS (NCT02270203) reports that 83% of patients are satisfied 3 years post treatment, which is very similar to the initial satisfaction rates of 84% reported.

Surgical revisions rates for the iFuse Implant System at 4 years and open surgery at 5 years were estimated based on an assumption that revision surgery rates were constant over the follow up period. Constant transition probabilities were used until the end of the model time horizon of 7 years. These assumptions were applied as revisions rates beyond these time points were not available. Assuming a uniform distribution means that the cost of revision surgeries is spread over time when in practice this may have been front loaded. This assumption was not expected to bias the results as this same approach was applied in both arms.

All transition probabilities in the stepped pathway were also assumed to remain constant over 7 years. These assumptions were applied as very little data is reported on long term use of steroid injection and RF ablation procedures. Wide confidence intervals were applied to explore the impact of this assumption on the costs and clinical outcomes in sensitivity analysis.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The impact of treating adverse events was not explicitly captured in the model as the impact of treating adverse events was assumed to be captured through prolonged procedures times, longer length of stays and revision surgeries. This approach is consistent with other economic models assessing the cost-effectiveness of the iFuse Implant System.[83]

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Two surgical consultants were interviewed to provide feedback on the following:

- To validate the inputs sourced from clinical trials for the procedure times, length of stay and revision rates with the iFuse Implant System, anterior open surgery and posterior open surgery
- To validate the inputs sourced from clinical trials for the proportion of patients with a good response following surgery with the iFuse Implant System, anterior open surgery and posterior open surgery
- To validate the equipment cost assumptions applied in the model for the iFuse Implant System and both types of open surgery
- To obtain feedback on any other resource use implications to the NHS associated with performing iFuse MIS or open surgery procedures that should be considered in the model or highlighted in this submission

Two pain management consultants were also interviewed to provide feedback on the following:

- To obtain feedback on standard of care within a stepped treatment pathway for treating SIJ pain

- The validate our approach to modelling the cost of a stepped treatment pathway
- To obtain assumptions for response rates and discontinuation rates for steroid injections and RF ablation

The criteria for selecting experts was based on their experience providing relevant treatments and willingness to participate in this research. 3 surgical consultants were contacted and 2 agreed to be interviewed. 2 pain management consultants were contacted both of whom agreed to be interviewed. None of those interviews were expected to have a conflict of interest or stated any. Declarations of conflict of interest were not explicitly sought.

Method used for interviews

All of the interviews were conducted by an independent researcher commissioned by SI-BONE. Three of the interviews were conducted by telephone and one was conducted face-to-face. Two topic guides were developed for the interviews with surgical and non-surgical consultants respectively. This provided an opening statement to give context to the purpose of the interview and listed a series of open and closed questions.

Appendix B provides a list of the experts consulted, the topic guides, and a summary of the feedback provided.

In addition to conducting interviews, the SI-BONE team consulted with hospital staff directly and by email to obtain unit costs from current price lists for consumables used to perform open surgery.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C6 below.

Table C6: Summary of variables applied in the cost model

Variable	Value	Range or 95% CI (distribution)	Source
Model Transition Probabilities (biannual)			
% Good Response to Treatment: iFuse	0.84	0.798 - 0.882 (Beta)	Zaidi et al.[55]
% Good Response to Treatment: Open Surgery	0.54	0.455 - 0.625 (Beta)	Zaidi et al.[55]
% Good Response to Treatment: Steroid Injection	0.50	0.20 – 1 (Beta)	UK clinician feedback
% Good Response to Treatment: RF Ablation	0.20	0 - 0.50 (Beta)	UK clinician feedback
% Good Response to Treatment: Revision Surgery	0.50	0.21 - 0.63 (Beta)	Assumption
Steroid Injection to No Treat	0.084	0 - 0.20 (Beta)	UK clinician feedback
Steroid Injection to RF Ablation	0.069	0 - 0.20 (Beta)	UK clinician feedback
RF Ablation to No Treat	0.293	0.10 - 0.50 (Beta)	UK clinician feedback
Surgical Revision Probability: iFuse	0.031	0.31 - 0.055 (Beta)	Cher et al.[83]
Surgical Revision Probability: Open Surgery	0.016	0.09 - 0.0541 (Beta)	Zaidi et al.[55]
Non-Surgical Costs			
Procedures in 6 Months: Steroid Injections	1.5	1.0 - 3.0 (Log Normal)	UK clinician feedback
Procedures in 6 Months: RF Ablation	0.25	0.25 - 0.50 (Log Normal)	UK clinician feedback
Procedure Cost: Steroid Injection	£637.69	£383.72 - £841.85 (Gamma)	NHS reference cost 2015-16[97]
Procedure Cost: RF Ablation	£773.67	£511.64 - £995.56 (Gamma)	NHS reference cost 2015-16[97]
Pain Management Cost	£474.72	£94.25 - £855.19 (Gamma)	Calculated using drug cost assumptions[98] and clinician cost assumptions[99]
Surgical Costs			
Procedure Time: iFuse	59	50.9 - 66.9 (Log Normal)	Heiney et al.[54]
Procedure Time: Open Surgery Anterior	104	73 – 180 (Log Normal)	Ledonio et al.[46] Nyström et al.[96]
Procedure Time: Open Surgery Posterior	163	138 – 188 (Log Normal)	Smith et al.[44]
Unit Cost of Surgery (per minute)	£17.03	£6.39 - £27.67 (Gamma)	ISD Scotland[100]

Length of Stay: iFuse	1.7	1.2 - 2.2 (Log Normal)	Heiney et al.[54]
Length of Stay: Open Surgery Anterior	8.0	2.0 - 9.0 (Log Normal)	Ledonio et al.[46] Nyström et al.[96]
Length of Stay: Open Surgery Posterior	5.1	1.4 – 8.8 (Log Normal)	Smith et al.[44]
Unit Cost of Hospital Stay: iFuse	£272.32	£201.63 - £337.79 (Gamma)	NHS reference cost 2015-16[97]
Unit Cost of Hospital Stay: Open Surgery	£380.99	£260.59 - £437.18 (Gamma)	NHS reference cost 2015-16[97]
% Open Surgery Anterior	50%	0 - 100% (Beta)	Assumption
Training Hours: iFuse	4	3 – 5 (Log Normal)	Assumption
Number of Surgeries in 5 Years: iFuse	90	70 – 110 (Log Normal)	Assumption
Surgeon Hourly Cost	£137	£132.89 - £213.72 (Gamma)	Unit Costs of Health and Social Care 2016[99]
Consumable Costs: Anterior	£1,220	£976 - £1464 (Gamma)	Calculation using resource reported in Ledonio et al.[46], unit costs from unpublished UK price lists
Consumable Costs: Posterior	£3,300	£2640 - £3960 (Gamma)	UK Clinician
Consumable Costs: iFuse	£4059	£3248 - £4871 (Gamma)	Calculation using resource use assumptions provided by Si-Bone and the UK price list provided by SI-BONE
Unit Cost Follow-up: Pre-assessment	£177.27	£106.74 - £220.21 (Gamma)	NHS reference cost 2015-16[97]
Unit Cost Follow-up	£131.21	£78.98 - £159.40 (Gamma)	NHS reference cost 2015-16[97]
Number of Follow-up Visits: iFuse	4	3 – 5 (Log Normal)	Assumption
Number of Follow-up Visits: Open Surgery	4	3 – 5 (Log Normal)	Assumption

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The iFuse Implant System is currently coded under the following HRG NHS reference costs for 2015/2016.

Table C7: HRG codes for iFuse Implant System

HRG	Description	Activity	Ref cost
HN13A	Major Hip Procedures for Non-Trauma, 19 years and over, with CC Score 10+	9	£ 24,189.84
HN13B	Major Hip Procedures for Non-Trauma, 19 years and over, with CC Score 6-9	46	£ 12,798.19
HN13C	Major Hip Procedures for Non-Trauma, 19 years and over, with CC Score 4-5	86	£ 10,558.84
HN13D	Major Hip Procedures for Non-Trauma, 19 years and over, with CC Score 2-3	222	£ 8,453.05
HN13E	Major Hip Procedures for Non-Trauma, 19 years and over, with CC Score 1	320	£ 5,616.10
HN13F	Major Hip Procedures for Non-Trauma, 19 years and over, with CC Score 0	1,040	£ 4,486.54

In the model, a bottom up approach was applied to calculate the cost of the iFuse Implant System as the HRG codes listed above include procedures other than the iFuse Implant System for treating SIJ pain. The weighted average cost of these HRG codes may therefore be skewed by higher volumes of other surgical procedures included under the same HRG codes. Furthermore, applying a bottom up approach facilitated a more like for like comparison of the cost of the iFuse Implant MIS compared to open surgery.

Open surgery procedures for SIJ fusion are currently coded under the following HRG reference costs:

Table C8: HRG codes for SIJ fusion surgery

HRG	Description	Activity	Ref cost
HC60A	Very Complex Extradural Spinal Procedures with CC Score 4+	194	£ 12,254.98
HC60B	Very Complex Extradural Spinal Procedures with CC Score 2-3	469	£ 9,605.42
HC60C	Very Complex Extradural Spinal Procedures with CC Score 0-1	1,509	£ 8,430.34
HC61A	Complex Extradural Spinal Procedures with CC Score 4+	260	£ 11,746.78

HC61B	Complex Extradural Spinal Procedures with CC Score 2-3	600	£ 7,865.56
HC61C	Complex Extradural Spinal Procedures with CC Score 0-1	1,361	£ 7,143.80
HC62A	Very Major Extradural Spinal Procedures with CC Score 4+	393	£ 8,654.36
HC62B	Very Major Extradural Spinal Procedures with CC Score 2-3	1,039	£ 6,541.34
HC62C	Very Major Extradural Spinal Procedures with CC Score 0-1	2,395	£ 5,941.48
HC63A	Major Extradural Spinal Procedures with CC Score 4+	509	£ 7,062.56
HC63B	Major Extradural Spinal Procedures with CC Score 2-3	1,400	£ 5,361.21
HC63C	Major Extradural Spinal Procedures with CC Score 0-1	3,641	£ 4,780.18
HC64A	Intermediate Extradural Spinal Procedures with CC Score 4+	727	£ 5,898.15
HC64B	Intermediate Extradural Spinal Procedures with CC Score 2-3	2,301	£ 4,742.55
HC64C	Intermediate Extradural Spinal Procedures with CC Score 0-1	8,313	£ 4,142.34
HC53A	Very Major Spinal Reconstructive Procedures with CC Score 4+	118	£ 18,270.97
HC53B	Very Major Spinal Reconstructive Procedures with CC Score 2-3	247	£ 12,442.09
HC53C	Very Major Spinal Reconstructive Procedures with CC Score 0-1	532	£ 10,791.89
HC54A	Major Spinal Reconstructive Procedures with CC Score 4+	241	£ 15,051.40
HC54B	Major Spinal Reconstructive Procedures with CC Score 2-3	455	£ 10,112.53
HC54C	Major Spinal Reconstructive Procedures with CC Score 0-1	1,143	£ 9,441.98

Like the iFuse Implant System, a bottom up approach was applied to calculate the cost of open surgery stratifying by anterior and posterior approach and assuming a 50:50 split. The weighted average of the HRG codes listed above was not applied as these HRG codes include surgeries other than open fusion surgery for SIJ pain. Furthermore, as noted above using a bottom up approach facilitated a more like for like comparison with the cost of iFuse MIS.

The OPCS codes, HRG codes and reference costs used for steroid injections in patients with a diagnosis of SIJ pain are described in the diagram below.

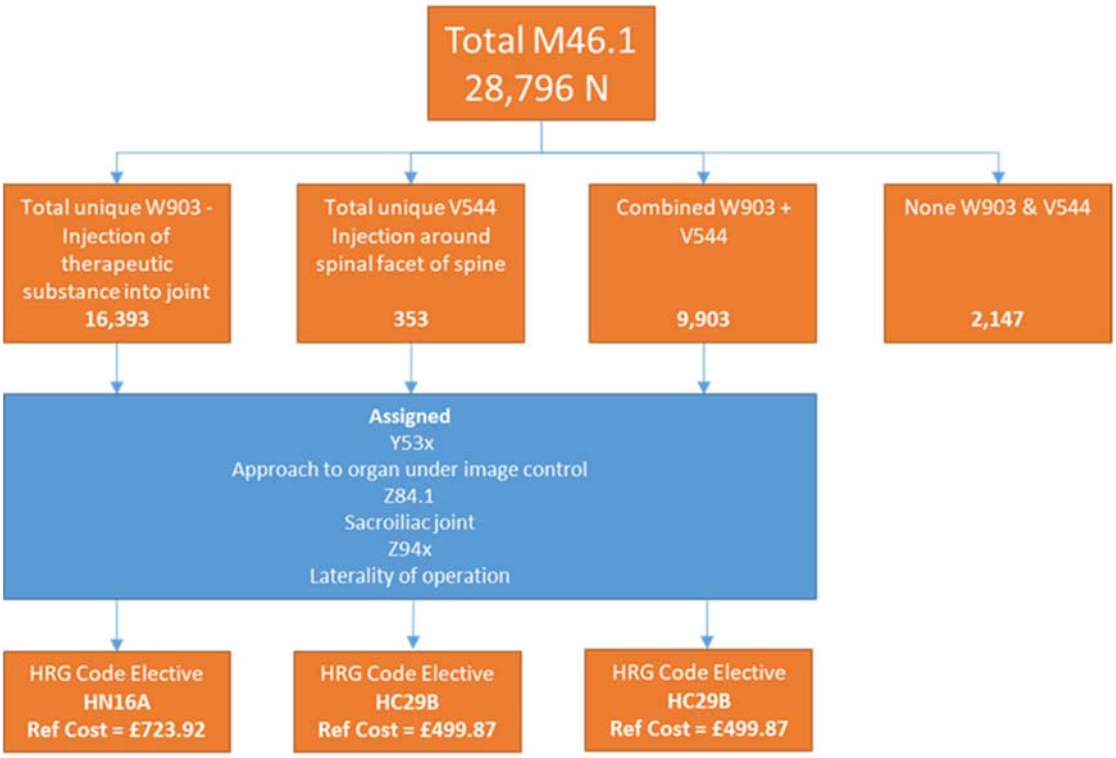


Figure 16 – OPCS codes, HRG codes and reference costs used for Steroid Injections in patients with a diagnosis of SIJ pain[101]

The HGR codes for RF Ablation are as follows:

Table C9: HRG codes for RF Ablation therapy

HRG	Description	Activity (outpatient)	Ref cost
AB15Z	Radiofrequency Ablation or Cryoablation, for Pain Management	11,006	£ 925.80
AB16Z	Denervation or Injection Around Spinal Facet, for Pain Management	38,000	£ 729.61

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

- An open surgical procedure with fusion can be coded using the following OPCS codes: V294, V304, V333, V335, V336, V343, V345, V346, V38, V39, V40, V66, V512

- An iFuse MIS procedures can be coded using the following OPCS codes:
    - W62.1 - Primary arthrodesis and internal fixation of joint NEC
    - Y53x - Approach to organ under image control
    - Z84.1 - Sacroiliac joint
    - Z94x - Laterality of operation
- RF ablation procedures can be coding using the following OPCS codes: V48X
- SI injection procedures may be coded using the following OPCS codes: W903 and V544
- PLIF procedures can be coding using the following OPCS codes: V385

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Specific searches were not carried out to source the cost inputs. Instead these were sourced from NHS references costs widely used in economic evaluations or internal market data collected by SI-BONE. All costs were vetted with UK experts and where there was uncertainty this was considered in the range applied in the sensitivity analysis.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

The summary of the methodology for obtaining or vetting resource use assumptions from clinical experts via structured interviews was described in section 9.2.5, with further details provided in appendix B.

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

The 2016-2017 list price for the consumables required to conduct iFuse MIS in the NHS is as follows:

Table C10: iFuse Implant System price list

Description	Unit cost	Units required per procedure	Source
Surgical Implants	£1,155.00	3	Assumptions for consumables provided by Si-Bone based on average use. Unit costs based on UK price list provided by Si-Bone
Surgical Accessories	£275.00	1	
Steinmann pins	£47.00	3	
Exchange pin	£47.00	1	
Surgical Drill	£131	1	
Total cost per procedure	£4059		

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

Not applicable. All prices reflect current NHS list prices.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C11 and C12. Table C12 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

Table C11: Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Theatre and Hospital Costs per iFuse Procedure		
Procedure Time (P, min)	59	Heiney et al.[54]
Cost of Theatre Time (T, £/min)	£17.03	ISD Scotland[100]
Length of Stay (L, day)	1.7	Heiney et al.[54]
Cost of Bed Day (B, £/day)	£272.32	NHS reference cost 2015-16[97] Weighted average cost of elective, excess bed days for back pain interventions HC53,54,60,61,62,63,64
= PT + BL	£1,4671.71	
Consumables for iFuse per iFuse Procedure		
Surgical Implants	3 x £1,155.00	SI-BONE List Price
Surgical Accessories	£275.00	SI-BONE List Price
Steinmann Pins	3 x £47.00	SI-BONE List Price
Exchange Pin	£47.00	SI-BONE List Price
Drill	£131.00	SI-BONE List Price
Total	£4,059.00	
Training Cost per iFuse Procedure		
Training Hours (H, per surgeon)	4	Assumption provided by SI-BONE
Unit Cost Surgical Consultant (S, £/hr)	£137.00	PSSRU[99]
Number of Surgeries per surgeon in 5 years (N)	90	UK Clinician Feedback
= HS / N	£6.09	
Follow Up Cost per Procedure		
Number of Follow up Visits (N)	4	UK Clinician Feedback
Unit Cost Pain Management Assessment 1st visit (P1, £)	£177.27	NHS reference cost 2015-16[97] WF01B: Non-Admitted Face to Face Attendance, First; Service code 191; Pain Management
Unit Cost Pain Management Assessment (P2, £)	£131.21	NHS reference cost 2015-16[97] WF01A - Non-Admitted Face to Face Attendance, Follow up; Service code 191; Pain Management
= P1 + ((N - 1) * P2)	£570.90	
Total cost per treatment/patient	£6,103.70	

Table C12: Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Anterior Open Surgery		
Theatre and Hospital Costs per Procedure		
Procedure Time (P, min)	104	Ledonio et al.[46]
Cost of Theatre Time (T, £/min)	£17.03	ISD Scotland[100]
Length of Stay (L, day)	8.0	Ledonio et al.[46]
Cost of Bed Day (B, £/day)	£380.99	NHS Reference cost 2015-16[97] Weighted average cost of elective, excess bed days for back pain interventions HN13 A-F
= PT + BL	£4,819.04	
Consumables Costs per Procedure		
Two plates and eight screws	£500.00	UK Clinician
One cannulated screw with washer	£100.00	
One drain	£60.00	
One DBM	£500.00	
Three Stiches	£60.00	
Total	£1,220.00	
Follow Up Costs per Procedure		
Number of Follow up Visits (N)	4	UK Clinician Feedback
Unit Cost Pain Management Assessment 1st visit (P1, £)	£177.27	NHS reference cost 2015-16[97] WF01B: Non-Admitted Face to Face Attendance, First; Service code 191; Pain Management
Unit Cost Pain Management Assessment (P2, £)	£131.21	NHS reference cost 2015-16[97] WF01A - Non-Admitted Face to Face Attendance, Follow up; Service code 191; Pain Management
= P1 + ((N - 1) * P2)	£570.90	
Total cost per treatment/patient	£6,609.94	
Items	**Value**	**Source**
Posterior Open Surgery		
Theatre and Hospital Costs per Procedure		
Procedure Time (P, min)	163	Smith et al.[44]
Cost of Theatre Time (T, £/min)	£17.03	ISD Scotland[100]
Length of Stay (L, day)	5.1	Smith et al.[44]

Cost of Bed Day (B, £/day)	£380.99	*NHS Reference cost 2015-16*[97] *Weighted average cost of elective, excess bed days for back pain interventions HN13 A-F*
= PT + BL	£4,718.94	
Consumables Costs per Procedure		
Two pedicle screws	£800.00	*Smith*[90]*, unpublished UK list prices*
One cross connecting rod	£250.00	
One PLIF cages	£900.00	
One BMB sponge	£1,200.00	
Two crew caps, nuts etc	£150.00	
Total	£3,300.00	
Follow Up Costs per Procedure		
Number of Follow up Visits (N)	4	*UK Clinician Feedback*
Unit Cost Pain Management Assessment 1st visit (P1, £)	£177.27	*NHS reference cost 2015-16 WF01B: Non-Admitted Face to Face Attendance, First; Service code 191; Pain Management*
Unit Cost Pain Management Assessment (P2, £)	£131.21	*NHS reference cost 2015-16 WF01A - Non-Admitted Face to Face Attendance, Follow up; Service code 191; Pain Management*
= P1 + ((N - 1) * P2)	£570.90	
Total cost per treatment/patient	£8,589.84	

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

The resource use assumptions for each health state were aligned upon with internal and external clinical experts 9.2.1. A list of all sources used is described in **Table C13** below.

Table C13: List of health states and associated costs in the economic model

Health states	Items	Value	Reference
iFuse Surgery	**Technology cost**	£4,059.00	Table C6
	Hospital cost	£1,467.71	
	Training cost	£6.09	
	Follow up costs	£570.90	
	Early Revision Surgery	£26.34	
Open Surgery	**Technology cost**	£2,260.00	Table C6 50:50 anterior posterior split
	Hospital cost	£4,768.99	
	Follow up costs	£570.90	
	Early Revision Surgery	£122.51	Revision rate * surgery cost from Table C6 50:50 anterior posterior split
	Total	£7,722.40	
Good Response	**Total**	£0.00	Assumption
Chronic Pain	**Low medication cost**	£63.25	BNF[98] Daily Regimen = cocodamol 4 x 8/500 mg + naproxen 2 x 500 mg + Omeprazole 20 mg.
	High medication cost	£692.95	BNF[98] Daily Regimen = tapentadol 2 x 200 mg + naproxen 2 x 500 mg + Omeprazole 20 mg
	Unit cost GP visit	£31.00	PSSRU[99]
	Unit cost pain management outpatient	£131.21	NHS reference cost 2015-16[97] WF01A - Non-Admitted Face to Face Attendance, Follow up; Service code 191; Pain Management
	Total	£474.72	Assumes 50:50 split between low cost and high cost medication and strong opioids require outpatient consultation
iFuse Revision Surgery	**Technology cost**	£4,059.00	Table C6
	Hospital cost	£1,467.71	
	Follow up costs	£570.90	
	Total	£6,097.61	
Open Revision Surgery	**Technology cost**	£2,260.00	Table C6 50:50 anterior posterior split
	Hospital cost	*£4,768.99*	
	Follow up costs	*£570.90*	

	Total	£7,599.89	
1st Steroid Injection	**Number of procedures in 6 months**	1.5	UK Clinician
	Procedure cost	£637.69	NHS reference cost 2015-16[97] Weighted average of HC29B, HN16A by HES episode data for procedure codes W903 and V574
	Total	£956.54	
Repeat Steroid Injection	**Number of procedures in 6 months**	1.5	UK Clinician
	Procedure cost	£637.69	NHS reference cost 2015-16[97] Weighted average of HC29B, HN16A day cases by HES episode data for procedure codes W903 and V574
	Total	£956.54	
1st RF Ablation	**Number of procedures in 6 months**	0.25	UK Clinician
	Procedure cost	£773.67	NHS reference cost 2015-16[97] Weighted average of AB15Z, AB16Z day case procedures by activity volume
	Total	£193.42	
Repeat RF Ablation	**Number of procedures in 6 months**	0.25	UK Clinician
	Procedure cost	£773.67	NHS reference cost 2015-16[97] Weighted average of AB15Z, AB16Z day case procedures by activity volume
	Total	£193.42	

Adverse-event costs

9.3.9 Complete table C14 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost

model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Table C1: List of adverse events and summary of costs included in the cost model

Adverse events	Items	Value	Reference
iFuse Revision Surgery	**Technology cost**	£4,059.00	Table C6
	Hospital cost	£1,467.71	
	Follow up costs	£570.90	
	Total	£6,097.61	
Open Revision Surgery	**Technology cost**	£2,260.00	
	Hospital cost	£4,768.99	
	Follow up costs	£570.90	
	Total	£7,599.89	

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Social care costs and patient and carer costs have not been quantified in this cost analysis. The impact of the iFuse Implant system on these aspects is discussed in section 9.3.11 below.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

There is very likely to be a cost associated with the impact of long-term opioid use that it has not been possible to capture in the model. Chronic pain patients treated with opioids are likely to experience some, or all of the following side effects with consequent resource implications: respiratory depression, endocrine and immune effects, hypersensitivity to pain, and dependence and withdrawal.[88]

Although not considered in health economic evaluations in the UK, there are wider productivity considerations to patients experiencing chronic pain. Work productivity is reduced among patients who may have to miss work for clinical appointments, or because pain or disability prevents them from performing in their job. As the iFuse Implant System is demonstrated to significantly reduce the number patients with SI joint pain living in long-term chronic pain compared to all comparator treatments (open surgery and conservative

management), if these aspects were quantified it is expected that the cost-savings associated with the iFuse Implant System would be substantially higher.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

The cost analysis included both deterministic and probabilistic sensitivity analysis.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Both a deterministic and probabilistic sensitivity analysis were undertaken. The variables were varied according to plausible ranges: 95% confidence intervals were applied where this information was available, or other plausible ranges determined based on data availability.

Deterministic Sensitivity Analysis

Transition Probabilities

- The response to surgery for the iFuse Implant System was varied between 0.798 and 0.882 which is the 95% confidence interval for the trial data in Zaidi et al.[55]

- The response to surgery for Open Surgery was varied between 0.455 and 0.625 which is the 95% confidence interval for the trial data in Zaidi et al.[55]

- Response to steroids was varied between 0.20 to 1.00. This was intended to reflect the considerable uncertainty around this value. Clinician feedback from two UK clinicians indicated that somewhere between 40-70% of patient's benefit from repeat injections. To be conservative this range was extended to 20-100%.

- Response to RF ablation was varied between 0 to 0.50. This was intended to reflect the considerable uncertainty around this value. Clinician feedback from two UK clinicians indicated that somewhere between 15-30% of patient's benefit from repeat procedures. To be conservative this range was extended to 0-50%.

- Response to revision surgery was varied between 0.21 and 0.63. The base case value was taken to be 0.50 after Cher et al.[83] The range was set to be 25% at the lower and 75% at the upper, of the value for the first iFuse Surgical Implant surgery. This range was also applied to surgical revision in the open surgery case, even though it would likely be lower, to be conservative in our approach.

- The discontinuation rate of steroid injections was varied between 0 and 0.20. This range is not backed by any data but was deemed conservative.

- The rate of transition from steroid injections to RF ablation was varied between 0 and 0.20. This range is not backed by any data but was deemed conservative.

- The discontinuation rate from RF ablation was varied between 0.10 to 0.50. This range is not backed by any data but was deemed conservative.

- The surgical revision rate for the iFuse Implant System was varied between 0.031 and 0.055 which is the 95% confidence interval for the trial data in Cher et al.[83]

- Surgical revision rates for open surgery were varied between 0.009 and 0.051 which is the 95% confidence interval for the trial data in Zaidi et al.[55]

Non-surgical Costs

- The number of steroid injection procedures in six months was varied between 1 to 3. UK clinicians reported repeat injections of between 1 to 2 in a six-month period. However, recent guidance from a partnership between Bristol, North Somerset and South Gloucestershire Clinical Commissioning Groups Commissioning Group[102] limits the maximum number of injections to 3 in a six-month period so this was the upper end that was used for the sensitivity analy*sis.*

- The steroid injection cost was varied between £383.72 to £841.85. These were the NHS reference cost lower and upper quartile costs for HRG codes HN16A and HC29B, weighted by the HES data for OPSC codes W903 and V574. This analysis of data was provided by Device Access who have access to HES data 2016-17.[101]

- The RF ablation cost was varied between £511.64 and £995.56, the lower and upper quartiles of the weighted AB15Z, AB16Z day case procedures from the NHS reference cost data for 2015/2016.[97]

Surgical Costs

- The iFuse Surgical Implant procedure time was varied between 51 to 67 as this was the random effects meta-analysis 95% confidence interval reported in Heiney et al.[54]

- The anterior open surgery procedure time was varied between 73 to 180; this range was sourced from Ledonio et al.[46] because there was no range reported in Nyström et al.[96] and to capture the wider variation reported in Ledonio et al.[46]

- The posterior open surgery procedure time was varied between 138 to 188; this range was sourced from Smith et al.,[44] a systematic literature review of 9 studies.

- The unit cost of theatre time was varied between £6.39 to £27.67 per minute. This reflects the range across regions from ISD Scotland.[100]

- The iFuse Implant System length of stay was varied between 1.2 to 2.2; this was the random effects meta-analysis 95% confidence interval reported in Heiney et al.[54]

- The anterior open surgery length of stay was varied between 2 and 9. The lower limit is sourced from Ledonio et al.[46] and the upper bound is a conservative estimate.

- The posterior open surgery length of stay was varied between the 95% confidence intervals 1.4 and 8.8 as per the systematic literature review reported in Smith et al.[44]

- Unit costs of the iFuse Implant System surgery hospital stay was varied between £201.63 and £337.79 which was the weighted lower and upper quartile of the NHS reference costs[97] for elective cost of elective, excess bed days for back pain interventions HC53,54,60,61,62,63,64.

- The unit cost of open surgery was varied between £260.59 and £437.18 which was the weighted lower and upper quartile of the NHS reference costs[97] for cost of elective, excess bed days for back pain interventions HN13 A-F.

- The percentage split between anterior and posterior open surgery was varied between 0 and 100% to reflect the complete uncertainty around this data.

- All surgery consumable costs which were derived from a bottom up costing approach were varied between ±20%.

Follow Up Costs

- Assessment costs varied between the upper and lower quartiles of the NHS reference costs[97] from which they were sourced.

- The number of assessment visits varied between 3 and 5 based on feedback from a UK surgeon.

Training Costs

- The number of training hours was varied between 3 and 5. The base case value was 4 hours. This is based on manufacturer recommendation. Therefore, a relatively tight range was used on the sensitivity analysis.

- The number of surgeries in 5 years was varied between 70 and 110 to reflect uncertainty over the number of iFuse Surgical Implant surgeries a trained surgeon might perform.

- The unit cost of a surgical consultant's time was varied between £132.89 to £213.72 which was the difference between the London weighting and the non-London weighting in the PSSRU data.[99]

Probabilistic Sensitivity Analysis

Probabilities

All probabilities were modelled using a beta distribution. Where the n values from the source data were known these were used to compute alpha and beta. Where the n values were not known, and the data were sourced from clinical advice, a low value of 10 was used for n to incorporate the considerable uncertainty in the data.

Costs

Cost data was modelled using a gamma distribution.

- Where the data was sourced from NHS reference costs, the gamma distribution was defined by mapping the upper and lower quartiles as the 95% confidence intervals and calculating alpha and beta via a method of moments approach.

- Where the costs were estimated using a bottom up approach the variance was set to 20% of the mean and the alpha and beta were calculated again using a method of moments approach.

Times/number of visits

Time data was modelled using log normal distributions using the ranges from the DSA to calculate the 95% confidence interval to apply in the distribution.

Medication use with iFuse and repeat steroid injection

A multi-way scenario-based sensitivity analysis was conducted to explore the assumption that only patients in the chronic pain health states are on opioid based pain medication regimens and hence patients with good outcomes following MIS with the iFuse Implant System and patients on repeat treatments with steroid injections or RFA are not on any pain medication regimens.

Analysis of the pain medication use reported in the iMIA study (unpublished data) reported that 57.7% of patients recruited to the iFuse Implant System trial arm were on opioid based pain medication regimens at baseline. This reduced to 33.3% at 2 years of follow up. In the model deterministic base-case, 16% of patients are assumed to still be in chronic pain after MIS with the iFuse Implant system and therefore on an opioid based medication regimen. As this percentage was lower than the percentage of patients reported to be on medication at 2-year follow-up post MIS with iFuse, the proportion of patients with a good response on pain medication was increased from 0% to 20%. This then equated to 33% of the overall patients being on pain medication after MIS with the iFuse Implant System, to align with data in the iMIA study.

The iMIA study also reported that 46.9% of patients in the conservative management arm (which consisted on physical therapy, steroid injections and RF ablation) were on an opioid based regimen at baseline. This percentage did not change at follow-up. In this scenario it was therefore assumed that 46.9% of patients in the repeat steroid injection and repeat RF ablation health states were also on an opioid based pain medication regiment during treatment.

9.4.3 Complete table C15, C16, and/or C17 as appropriate to summarise the variables used in the sensitivity analysis.

Table C15: Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Model Transition Probabilities (biannual)		
% Good Response to Treatment: iFuse	0.84	0.798 - 0.882
% Good Response to Treatment: Open Surgery	0.54	0.455 - 0.625
% Good Response to Treatment: Steroid Injection	0.50	0.20 - 1
% Good Response to Treatment: RF Ablation	0.20	0 - 0.50
% Good Response to Treatment: Revision Surgery	0.50	0.21 - 0.63
Steroid Injection to No Treat	0.084	0 - 0.20
Steroid Injection to RF Ablation	0.069	0 - 0.20
RF Ablation to No Treat	0.293	0.10 - 0.50
Surgical Revision Probability (bi-annual): iFuse	0.043	0.031 - 0.055
Surgical Revision Probability (bi-annual): Open Surgery	0.016	0.009 - 0.0541
Non-Surgical Costs		
Procedures in 6 Months: Steroid Injections	1.5	1.0 - 3.0
Procedures in 6 Months: RF Ablation	0.25	0.25 - 0.50
Procedure Cost: Steroid Injection	£637.69	£383.72 - £841.85
Procedure Cost: RF Ablation	£773.67	£511.64 - £995.56
Pain Management Cost	£474.72	£94.25 - £855.19
Surgical Costs		
Procedure Time: iFuse	59	50.9 - 66.9
Procedure Time: Open Surgery Anterior	104	73 - 180
Procedure Time: Open Surgery Posterior	163	138- 188
Unit Cost of Surgery (per minute)	£17.03	£6.39 - £27.67
Length of Stay: iFuse	1.7	1.2 - 2.2
Length of Stay: Open Surgery Anterior	8.0	2.0 - 9.0
Length of Stay: Open Surgery Posterior	5.1	1.4 – 8.8
Unit Cost of Hospital Stay: iFuse	£272.32	£201.63 - £337.79
Unit Cost of Hospital Stay: Open Surgery	£380.99	£260.59 - £437.18
% Open Surgery Anterior	50%	0 - 100%
Training Hours: iFuse	4	3 - 5
Number of Surgeries in 5 Years: iFuse	90	70 - 110

Surgeon Hourly Cost	£137	£132.89 - £213.72
Consumable Costs: Anterior	£1,220	£976.00 - £1464.00
Consumable Costs: Posterior	£3,300	£2640.00 - £3960.00
Consumable Costs: iFuse	£4059	£3248.20 - £4871.80
Unit Cost Follow-up: Pre-assessment	£177.27	£106.74 - £220.21
Unit Cost Follow-up	£131.21	£78.98 - £159.40
Number of Follow-up Visits: iFuse	4	3 - 5
Number of Follow-up Visits: Open Surgery	4	3 - 5

Table C16: Variables used in multi-way scenario-based sensitivity analysis

Variable	***% on opioid based pain medication regimen***		
Health state	**Good response post-surgery with iFuse**	**Steroid injections**	**RFA**
Base case	0%	0%	0%
Scenario 1	20%	46.9%	46.9%

Table C17: Variable values used in probabilistic sensitivity analysis

Variable	Base-case value	Distribution
Model Transition Probabilities (biannual)		
% Good Response to Treatment: iFuse	0.84	Beta (244,46)
% Good Response to Treatment: Open Surgery	0.54	Beta (71,60)
% Good Response to Treatment: Steroid Injection	0.50	Beta (5,5)
% Good Response to Treatment: RF Ablation	0.20	Beta (2,8)
% Good Response to Treatment: Revision Surgery	0.50	Beta (5,5)
Steroid Injection to No Treat	0.084	Beta (0.84,9.16)
Steroid Injection to RF Ablation	0.069	Beta (0.69,9.31)
RF Ablation to No Treat	0.293	Beta (2.93, 7.07)
Surgical Revision Probability (bi-annual): iFuse	0.031	Beta (47,10953)
Surgical Revision Probability (bi-annual): Open Surgery	0.009	Beta (2,129)
Non-Surgical Costs		
Procedures in 6 Months: Steroid Injections	1.5	Log Normal (1-3)
Procedures in 6 Months: RF Ablation	0.25	Log Normal (0.25-0.50)
Procedure Cost: Steroid Injection	£637.69	Gamma (30,21)
Procedure Cost: RF Ablation	£773.67	Gamma (39,20)
Pain Management Cost	£474.72	Gamma (6,79)
Surgical Costs		
Procedure Time: iFuse	59	Log Normal (51-67)
Procedure Time: Open Surgery Anterior	104	Log Normal (73-180)
Procedure Time: Open Surgery Posterior	163	Log Normal (138-188)
Unit Cost of Surgery (per minute)	£17.03	Gamma (10,2)
Length of Stay: iFuse	1.7	Log Normal (1.2-2.2)
Length of Stay: Open Surgery Anterior	8.0	Log Normal (2-9)
Length of Stay: Open Surgery Posterior	5.1	Log Normal (3.2-7.0)
Unit Cost of Hospital Stay: iFuse	£272.32	Gamma (61,4)
Unit Cost of Hospital Stay: Open Surgery	£380.99	Gamma (72, 5)
% Open Surgery Anterior	50%	Beta (5,5)
Training Hours: iFuse	4	Log Normal (3-5)
Number of Surgeries in 5 Years: iFuse	90	Log Normal (70,110)

Surgeon Hourly Cost	£137	Gamma (44,3)
Consumable Costs: Anterior	£1,220	Gamma (25,49)
Consumable Costs: Posterior	£3,300	Gamma (25,132)
Consumable Costs: iFuse	£4059	Gamma (25,162)
Unit Cost Follow-up: Pre-assessment	£177.27	Gamma (38,5)
Unit Cost Follow-up	£131.21	Gamma (41,3)
Number of Follow-up Visits: iFuse	4	Log Normal (3-5)
Number of Follow-up Visits: Open Surgery	4	Log Normal (3-5)

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

Not applicable

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C18.

Table C18: Base-case results

	Total per patient cost (£)
Technology	
iFuse	*£7,319*
Open Surgery	*£11,592*
Stepped Pathway	*£7,644*
Recurrent Steroids	*£12,004*

9.5.2 Report the total difference in costs between the technology and comparator(s).

Table C19: Total difference in costs between the technology and comparators

Comparison	**Difference in cost per patient**	**Conclusions**
iFuse vs Open Surgery	-£4,273	Cost-saving
iFuse vs Stepped	-£325	Cost-saving
iFuse vs Recurrent Steroids	-£4,685	Cost-saving

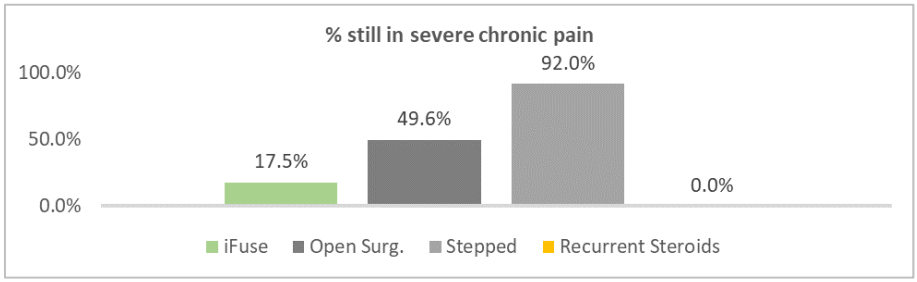


Figure 17 – Proportion of patients in chronic pain at 7 years for each comparator[2].

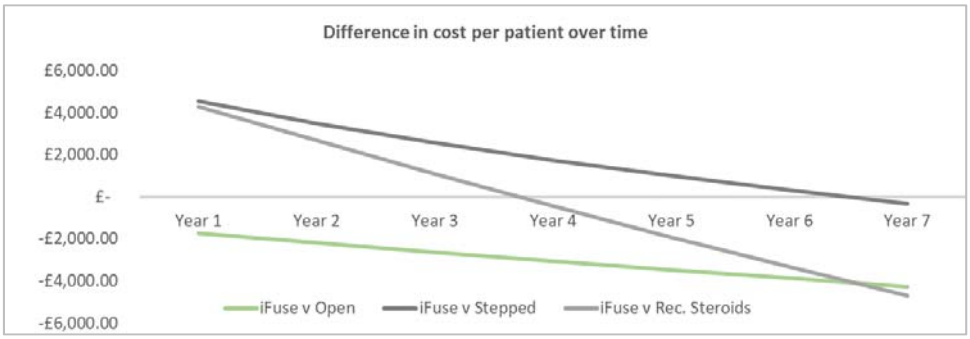


Figure 18 – Difference in cost per patient over time for each comparator versus iFuse

Compared to open surgery, MIS with the iFuse Implant System is expected to result in savings of over £4,000 per patient over a 7-year time horizon. Most of these savings accrue in the first year and are due to reduced time in theatre, faster patient recovery and lower risk of revision surgery which easily offset the higher consumable cost with the iFuse Implant System. Further savings also accrue over the medium and long term due to continued lower risk of revision surgery and lower probability of living in chronic pain managed by an opioid-base regimen.

Compared to the stepped pathway, MIS with the iFuse Implant System is also expected to be cost-saving after 7 years, albeit close to cost-neutrality. Surgery with the iFuse Implant system is more expensive in years 1 to 6 due to the higher upfront costs associated with a surgical procedure. After 6 years, MIS with the iFuse Implant system starts to be cost-saving as the annual

[2] *Note that 0% in the recurrent steroid arm is due to the assumption that patients on repeat steroid injection are assumed to not be in chronic pain when on treatment*

costs of repeat injections and chronic pain management are much higher than the average costs per patient beyond year 1 in patients treated with iFuse Implant System. If the time horizon was extended the cost-savings with the iFuse Implant System compared to the stepped pathway would continue to increase.

Similarly, to the stepped pathway, MIS with the iFuse Implant System is also expected to be cost-saving after 7 years when compared to a scenario that looks only at patients treated with repeat steroid injections. Here, cost-savings are achieved after year 4.

Furthermore, in all base-case comparisons, the likelihood of patients living in continued chronic pain is substantially lower in patients treated with MIS with the iFuse Implant system. In addition to the resource use implications of treating patients with chronic pain through pain clinics and medications, living with chronic pain has a detrimental impact on patients' quality of life.

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C20.

Table C20: Summary of costs by category of cost per patient

Item	Cost *iFuse*	Cost *Open Surgery*	Increment	Absolute increment	% absolute increment
Theatre & Hospital Costs	*£1,468*	*£4,769*	*£-3,301*	*£3,301*	*Mixed signs of increments mean that these formulas do not provide useful information.*
Consumable Cost	*£4,059*	*£2,260*	*£1,799*	*£1,799*	
Follow up	*£571*	*£571*	*£0*	*£0*	
Early Revision	*£26*	*£123*	*-£93*	*£93*	
Training Cost	*£6*	*£0*	*-£6*	*£6*	
Medical Pain Management	*£912*	*£2,594*	*-£1,682*	*£1,682*	
Revision Surgery	*£277*	*£1,276*	*-£999*	*£999*	
Total	*£7,319*	*£11,592*	*£-4,273*	*£4,273*	*100%*
	Cost *iFuse*	**Cost *Stepped***			
Theatre & Hospital Costs	*£1,468*	*£0*	*£1,468*	*£1,468*	*Mixed signs of increments mean that these formulas do not provide useful information.*
Consumable Cost	*£4,059*	*£0*	*£4,059*	*£4,059*	
Follow up	*£571*	*£0*	*£571*	*£571*	
Early Revision	*£26*	*£0*	*£26*	*£26*	
Training Cost	*£6*	*£0*	*£6*	*£6*	
Medical Pain Management	*£912*	*£4,087*	*-£3,175*	*£3,175*	

Revision Surgery	*£277*	*£0*	*£277*	*£277*	
Steroid Injections	*£0*	*£3,503*	*-£3,503*	*£3,503*	
RF Ablations	*£0*	*£54*	*-£54*	*£54*	
Total	*£7,319*	*£7,644*	*£325*	*£325*	*100%*
	Cost *iFuse*	**Cost Recurrent Steroids**			
Theatre & Hospital Costs	*£1,468*	*£0*	*£1,468*	*£1,468*	*Mixed signs of increments mean that these formulas do not provide useful information.*
Consumable Cost	*£4,059*	*£0*	*£4,059*	*£4,059*	
Follow up	*£571*	*£0*	*£571*	*£571*	
Early Revision	*£26*	*£0*	*£26*		
Training Cost	*£6*	*£0*	*£6*		
Medical Pain Management	*£912*	*£0*	*£912*	*£192*	
Revision Surgery	*£277*	*£0*	*£277*	*£277*	
Steroid Injections	*£0*	*£12,004*	*-£12,004*	*£12,004*	
RF Ablations	*£0*	*£0*	*£0*	*£0*	
Total	*£7,319*	*£12,004*	*-£4,685*	*£4,685*	*100%*
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing sub missions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C21.

Table C21: Summary of costs by health state per patient

Health state	Cost iFuse	Cost Open Surgery	Increment	Absolute increment	% absolute increment
Surgery	£6,130	£7,722	-£1,592	£1,592	37%
Mild Pain	£0	£0	£0	£0	0%
Chronic Pain	£912	£2594	-£1,682	£1,682	39.3%
Revision	£277	£1,276	-£999	£999	23.4%
Total	£7,319	£11,592	-£4,273	£4,273	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table C22: Summary of costs by health state in stepped pathway and recurrent steroid models

Health state	Cost Stepped Pathway	Cost Recurrent Steroids
1st Steroid Injection	£957	£0
Recurrent Steroid Injections	£2,547	£12004
Chronic Pain	£3,549	£0
1st RF Ablation	£34	£0
Repeat RF Ablation	£19	£0
Chronic Pain	£538	£0
Total	£7,644	£12,004

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C23.

Table C23: Summary of costs by adverse events per patient

Adverse event	Cost *iFuse*	Cost *Open Surgery*	Increment	Absolute increment	% absolute increment
Revision Surgery	*£303*	*£1,399*	*-£1,096*	*£1,096*	*100%*
Total	*£303*	*£1,399*	*-£1,096*	*£1,096*	*100%*
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

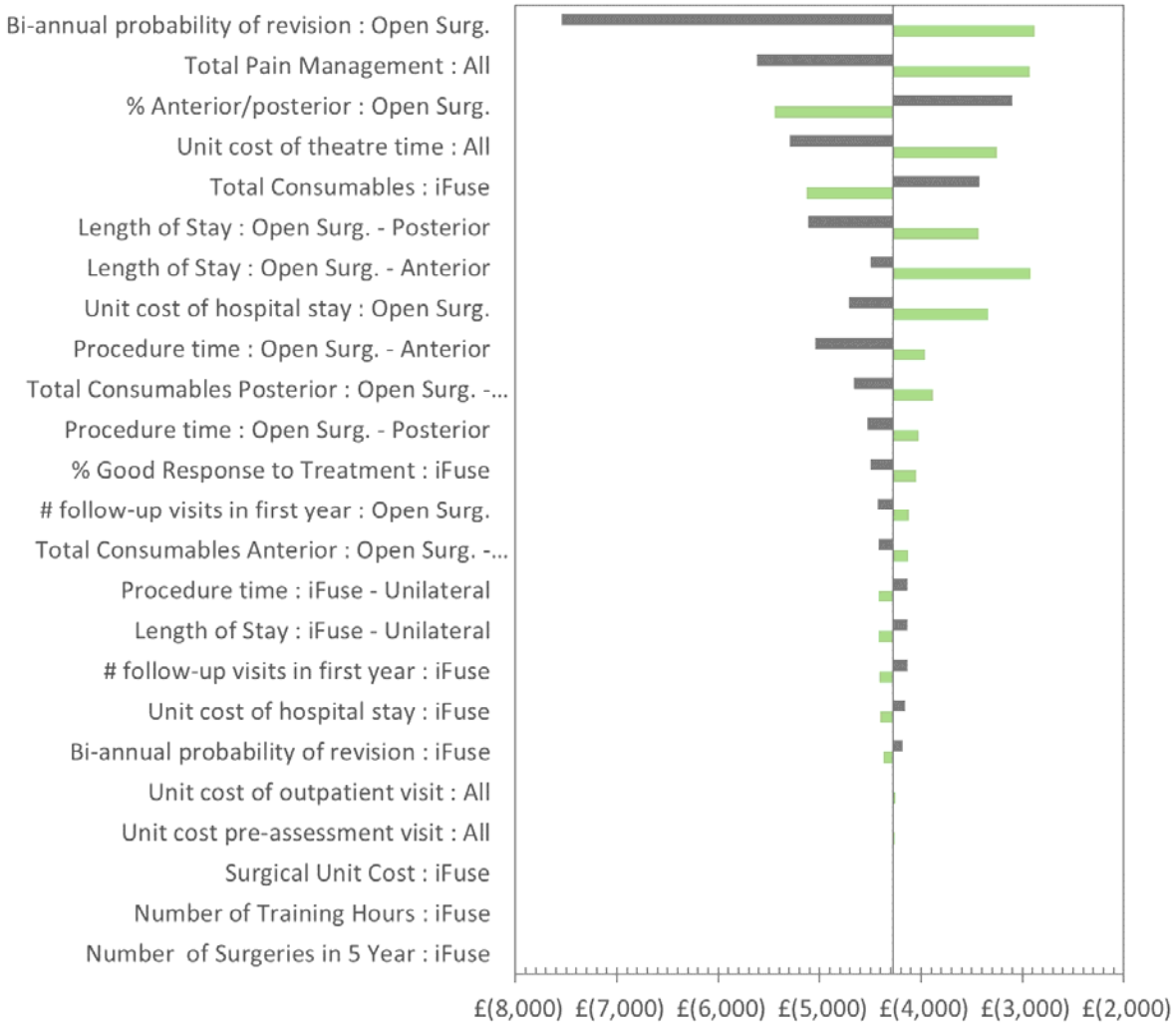


Figure 19 – Deterministic sensitivity analysis of iFuse vs open surgery

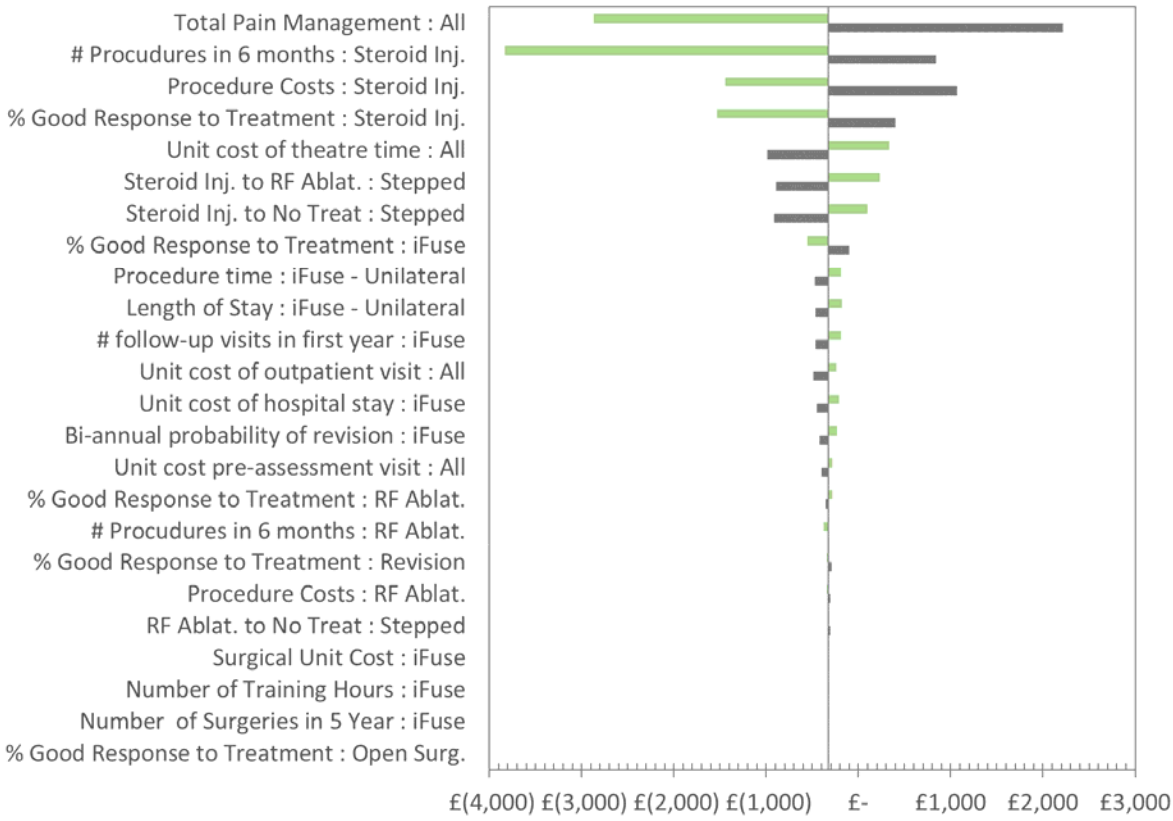


Figure 20 – Deterministic sensitivity analysis of iFuse vs stepped pathway

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Table C24: Results of deterministic multi-way scenario sensitivity analysis.

	Total per patient cost (£)
Technology	
iFuse	*£8,256*
Open Surgery	*£11,592 (No change)*
Stepped Pathway	*£8,521*
Recurrent Steroids	*£14,798*

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

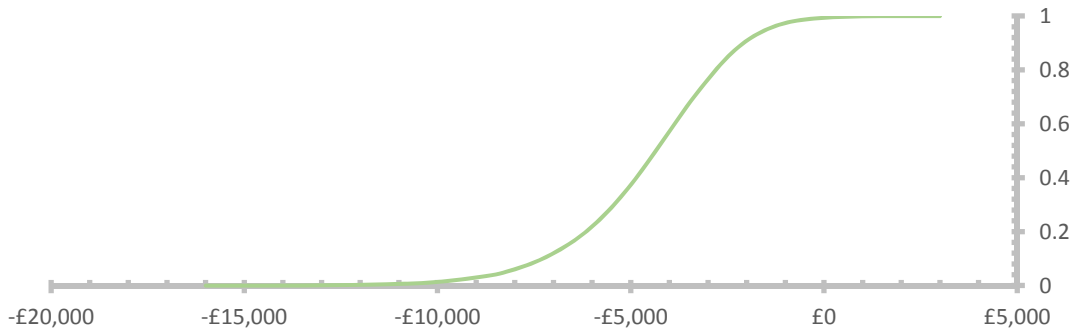


Figure 21 – Probabilistic sensitivity analysis of the cost increment of iFuse vs open surgery. iFuse has a 99.4% chance of being cost saving compared to open surgery.

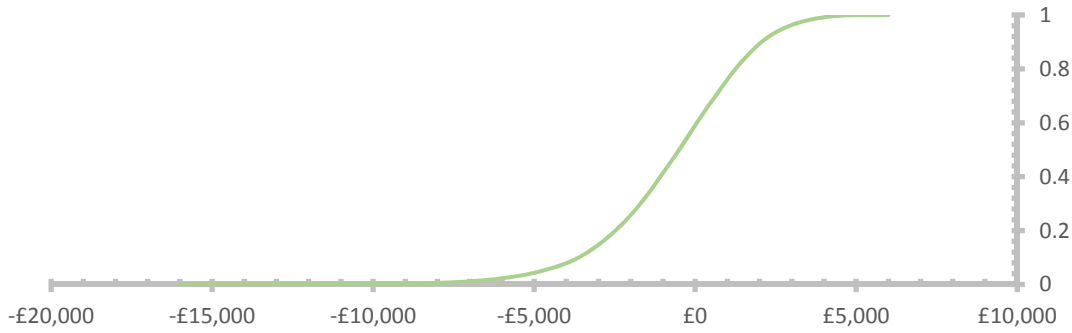


Figure 22 – Probabilistic sensitivity analysis of the cost increment of iFuse vs a stepped pathway. iFuse has a 59.1% chance of being cost saving compared to a stepped pathway.

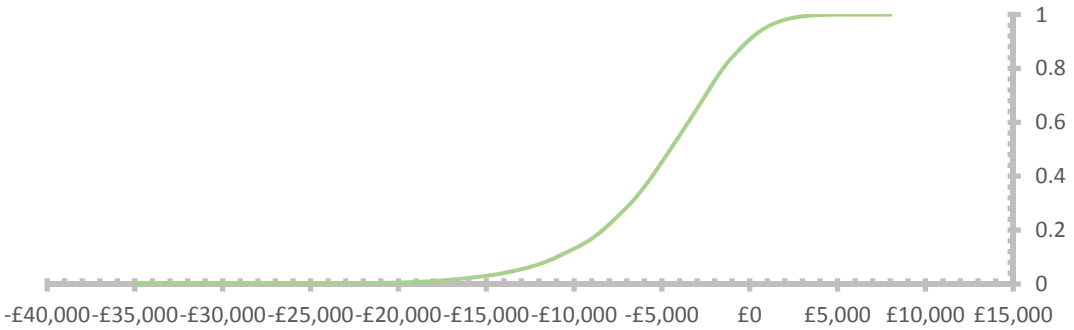


Figure 23 – probabilistic sensitivity analysis of the cost increment of iFuse vs a recurrent steroid use. iFuse has a 90.9% chance of being cost saving compared to a stepped pathway.

9.5.9 What were the main findings of each of the sensitivity analyses?

DSA – iFuse vs Open Surgery

Figure 19 indicates that when varying the inputs variables across their range, the cost increment of iFuse compared to open surgery is always negative: the cost increment varied from -£7,545 to -£2,920.

This result shows that even when the model's most sensitive parameters are set to their lowest conceivable values, iFuse still generates substantial cost saving compared to open surgery.

DSA – iFuse vs Stepped Pathway

Figure 20 indicates that there are seven values that when set to their extreme values, cause the cost increment of iFuse compared to the stepped pathway to become positive. The cost increment varied from -£3,828 to £2,220.

This result shows that the model is sensitive enough to seven of the input parameters, that the cost savings of iFuse compared to the stepped pathway are reversed. This highlights the requirement for probabilistic sensitivity analysis to quantify this uncertainty.

PSA – iFuse vs Open Surgery

Figure 21 highlights that there is a 99.4% probability that iFuse is cost saving compared to open surgery. The cost increment varied from -£15,572 to £2,249.

PSA – iFuse vs Stepped Pathway

Figure 22 highlights that there is a 59.1% probability that iFuse is cost saving compared to a stepped pathway. The cost increment varied from -£15,552 to £5,489. This result is somewhat expected based on the results of the deterministic sensitivity analysis.

There are several variables that when pushed to an extreme of their range have the effect of causing iFuse to become cost incurring relative to a stepped pathway.

However, the results of this probabilistic sensitivity analysis suggest that it is more likely that iFuse is cost saving than cost incurring compared to a stepped pathway.

PSA – iFuse vs Recurrent Steroids

Figure 23 highlights that there is a 90.9% probability that iFuse is cost saving compared to recurrent steroids. The cost increment varied from -£34,372 to £7,313.

9.5.10 What are the key drivers of the cost results?

iFuse vs Open Surgery

The top 5 model drivers in this case:

- **Bi-annual probability of revision**: the biannual probability of revision was varied from 0.00085 to 0.05406 and the respective cost increment range was -£2,882 to -£7,545. The range for this variable is quite large because of the trial from which the base case value is derived having an n of only 131. The upper value of the revision rate causes a high cost due to the required revision surgery, and results in higher medication costs associated with the poor surgical outcomes of the revision surgery. The combination of high uncertainty and degree of sensitivity makes this the key model driver.
- **Cost of pain management**: the cost of pain management was varied between £94.25 to £855.19 and the respective cost increment range was -£2,925 to £5,621. The higher cost of pain management favours

the technology with better surgical outcomes which results in fewer patients requiring pain management.

- **Percentage anterior/posterior open surgery**: the range was varied between 0% and 100% to reflect the very high degree of uncertainty around the data. This variable drives the model because a posterior surgery results in a cost increment of -£5,445 while anterior surgery results in a cost increment of -£3,101.

- **Unit cost of theatre time**: the range was allowed to vary from £6.38 per minute to £27.67 per minute and the respective cost increment range -£3,250 to -£5,296. Although this variable is applied in both arms of the comparison, the technology with a greater amount of theatre time required is penalised to a greater extent for having a higher unit cost of theatre time.

- **iFuse consumables cost**: although the cost of the iFuse consumables was only allowed to vary by +/- 20%, the model was quite sensitive to this relatively small range with a respective range of -£5,125 to -£3,421. This reflects the fact that a large part of the overall cost in the iFuse cost is made up of the consumables cost compared to the hospital costs.

iFuse vs Stepped Pathway

There are 7 model variables that when varied between upper and lower values result in the cost increment crossing the cost saving threshold (threshold = £0):

- **Cost of pain management**: the cost of pain management in the chronic pain health state was varied from £94.25 to £855.19 and the respective range of cost increment was £2,220 to -£2,870. The higher cost of pain management favours the technology with lower numbers of patients in the chronic pain health state.

- **Number of steroid procedures in six months**: the number of steroid procedures in a six-month period was varied between 1 and 3 and the respective cost increment range was £843 to -£3,828. The number of steroid procedures has a direct influence on the cost of being on steroid injections and an increase in this cost increases the cost of the stepped pathway.

- **Steroid injection procedure cost**: the steroid injection procedure cost was varied from £384 to £842 per procedure and the respective cost

increment ranged from £1,070 to -£1,447. An increase in this cost increases the cost of the stepped pathway compared to iFuse surgery.

- **Percentage of patients who respond well to steroid injections:** the percentage of patients who respond well to steroid injections was varied between 20% to 100% and the respective cost increment range was £398 to -£1,530. This variable influences the number of people who transition to a chronic pain state after their 1st steroid injection. When more patients go to the more expensive recurrent steroid injection health state (cf. chronic pain), the cost increment becomes more negative compared to iFuse surgery.

- **Unit cost of theatre time:** the unit cost of theatre time was varied between £6.39 to £27.67 per minute and the respective cost increment range was £-984 to £334. Because this variable forms a large component of the costs for the iFuse surgery case it has a relatively large effect on the cost increment.

- **Probability that a patient transitions from steroid injections to RFA:** the transition probability was varied between 0 and 0.20 and the respective cost increment range was -£892 to £233. The higher the probability that patients transition to RF ablation the more likely they will be to end in a chronic pain state because RF ablation had a higher discontinuation rate in the model. As the chronic pain state is less expensive than either of the procedure costs this makes the cost of the stepped pathway less expensive.

- **Probability that a patient transitions from steroid injections to chronic pain:** the transition probability was varied between 0 and 0.2 and the respective cost increment range was -£915 to £103. The higher the probability that patients discontinue steroid treatment the more likely they are to move to a cheaper chronic pain state which makes the stepped pathway less expensive.

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

Not applicable

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

No subgroups were considered in this analysis

9.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable

9.6.3 Describe how the subgroups were included in the cost analysis.

Not applicable

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

Not applicable

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Internal validation of the model was performed via systematic quality control procedures. The model was originally developed by a first modeller for early stage results. This model was then extended by a second modeller, who ensured the model structure and inputs were appropriate to the decision problem and performed sensitivity analysis. When the model was complete, two more reviewers gave feedback on the model structure and inputs.

External model validation was undertaken in a number of ways. Clinical feedback on the model inputs is found in Appendix B. Clinicians were asked to verify inputs such as procedure times found in the clinical evidence and were asked to provide and validate any assumptions used where no data was available.

- A bottom up costing approach was used for the surgical procedures for iFuse surgery, anterior and posterior open surgery due to the complexity of the clinical coding for these procedures.
- The bottom up costing approach can be compared to a weighted average approach using NHS reference costs.[97]

- The iFuse implant System surgery falls into the following HRG codes: HN13A, HN13B, HN13C, HN13D, HN13E, and HN13F which refer to "Major Hip Procedures for Non-Trauma, 19 years and above…" with varying CC scores.

- A weighted average of these codes by their activity data for 2015/2016 yield a procedure cost of £5,835. This is compared to a procedure cost calculated using the bottom up approach of £6,130.

- Open surgery falls into a very wide number of spinal surgery HRG codes. Spinal fusion could potentially fall into HC60A, HC60B, HC60C, HC61A, HC61B, HC61C, HC62A, HC62B, HC62C, HC63A, HC63B, HC63C, HC64A, HC64B, HC64B, HC64C, HC53A, HC53B, HC53C, HC54A, HC54B, or HC54C.

- A weighted average of these codes by their activity data for 2015/2016 yield an average procedure cost of £6,093. This is compared to a bottom up approach which yields a procedure cost of £7,722. However, this cost is averaged across a 50:50 split of anterior and posterior surgeries. When looking at anterior only the cost is £6,717 and when looking at posterior only the cost is £8,728. These codes incorporate a wide range of spinal procedures and so the bottom up numbers used in the model are expected to be more valid. The uncertainty in the values that make up these numbers is explored in the sensitivity analysis.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

In general, the results are consistent with the academic literature. Section 8 identified 5 previous economic evaluations which were undertaken from various stakeholder perspectives in the US. The earliest study identified, Ackerman et al.,[76] presented cost savings over a patient's lifetime of $3,358 of MIS SI joint fusion compared to non-operative care.

In 2014 Ackerman et al.[79] published an analysis of MIS SI joint fusion compared to non-operative care in the US over a 10-year time horizon (as a sensitivity analysis). Cost neutrality was achieved at 6 years. MIS costs were

largely accrued in year 1 and non-operative care costs were accrued over time. Although, the health care costs from a US perspective may be quite different from a UK perspective, the current model agrees very well with the cost neutrality time point. The current model achieves cost neutrality somewhere between 6 and 7 years.

In Cher et al.,[83] a USA cost utility model was presented that found that MIS Si joint fusion was cost effective compared to non-operative care over a 5-year time horizon. Their finding was that it was not until 13 years that cost neutrality between the two approaches was achieved. This is a longer time than the current UK model. However, there are two factors that have the potential to drive this difference: the first is that medication costs are not considered in the Cher et al. study; and the second is that they applied a conservative reduction in non-operative costs over time though they acknowledge this is counter to the available evidence.

The remaining two studies identified, Saavoss et al.[84] and Polly et al.[28] do not present models with which the current evaluation is directly comparable. Saavoss et al. presents the improvement in worker productivity due to MIS SI joint fusion and Polly et al. models the strategy of including the SIJ in the preoperative workup of chromic lower back pain.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes, the cost analysis is relevant to all patients with unresolved SIJ pain where conservative management has been unsuccessful.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Strengths

- The analysis agrees well with the previous economic evaluations within the literature. A particular strength of this analysis is that this is the first comparison of MIS SI joint fusion compared to open surgery and non-operative care from a UK NHS perspective.

- All of the inputs for resource use have been sourced from a UK NHS perspective using a combination of bottom-up procedure pricing and NHS reference costs where appropriate.

- The surgical procedure costs for this analysis were calculated on a like for like bottom up approach. However, they were cross-validated against a weighted average approach using NHS reference cost data for 2015/2016.[97]

- The model structure was designed to capture costs and outcomes for both surgical and non-operative care. The model allowed the comparison of MIS SI joint fusion technology with other treatments in three different scenarios: (1) open surgery using both anterior and posterior approaches; (2) a non-operative stepped treatment pathway; and (3) patients who rely on recurrent steroid injections to manage their pain.

- This analysis conducted sensitivity analysis on all of the variables included in the model. Both deterministic and probabilistic methods were used. The results showed that although there was considerable uncertainty in some of the data, the main cost drivers were identified. The results can be considered robust by the fact that against all three treatment strategies, it is more probable that MIS SI joint fusion is cost saving than cost incurring.

Weaknesses

- The major weakness of this analysis is that there is considerable uncertainty in the some of the model parameters that the cost increment is most sensitive to, including:

    - Transition probabilities through the stepped pathway which were based on clinical input only and likely to be highly variable

    - The cost of pain management which is likely to be highly heterogeneous across patients with chronic pain

    - The procedure times and length of hospital stays associated with the different surgical procedures are based on data from clinical trials and are unlikely to incorporate the learning curve that surgeon utilising a new technique might go through. Feedback from surgeon performing procedures with the iFuse Implant System suggest that with experience the procedures times may be considerably shorter than the times applied in this analysis.

- Although the primary model comparison was made with iFuse Implant System compared to open surgery, it is unclear in practise how many surgeons are using an open surgical approach and whether they undertake this anteriorly or posteriorly.

- The model assumes that patients who receive a benefit from iFuse Implant System surgery continue to do so throughout until the end of the 7-year model time horizon. Although the data so far shows that this is likely to be the case this has only been evaluated at up to 3 years follow up and longer time trials are still ongoing.

- In the base case analysis opioid use is only accounted for in patients who reside in chronic pain states. In a recent analysis of the opioid use of patients in the iMIA clinical trial, Dengler et al.[103] showed that opioid use in patients who undertook iFuse surgery went from 57.7% at baseline to 44.2% at six-months. Recent unpublished analysis of the iMIA data showed that at two-years post operation, opioid use had further decreased to 33.3%. Dengler et al. also showed a statistically significant reduction in opioid dose from 73.9 mg oral morphine equivalent daily dose at baseline to 51.1 mg at 6 months. The effect of this simplifying, but incomplete assumption that opioid use is only accounted for in chronic pain states, is unclear. Although it is likely that medication cost in the surgical treatment arms is not being accounted for, this is also the case for patients on treatment in the stepped pathway and recurrent steroid use arms. Dengler et al. observed no significant difference in the conservative management arm of the iMIA trial in opioid use at baseline and at 6 months, so although the assumption that after surgery patients completely stop taking opioid medication is false, there is at least a definite reduction in the amount of opioid use in the iFuse group. In contrast there was not an observable reduction in the non-operative care group. The multi-way sensitivity analysis in section 9.6 attempts to evaluate this scenario and indicates that including opioid medication use for good responders to treatment and for those patients on non-operative treatments (steroid injections and RF ablation) would have very little impact on the conclusions for the comparison of iFuse with either open surgery and the stepped pathway.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further research to enhance the robustness of the results would be centred around reducing the uncertainty around key data: namely, the structure and likelihood of transition between points on the stepped pathway; further research into the average cost of pain medication for patients in all health states; and further research into the resource use of surgery in real world settings.

Section C: Appendix A - Examples of anterior and posterior open surgical techniques

Example of anterior open fusion surgery (Nyström et al.[96]*)*

The SIJ is accessed via anterior transverse abdominal incision, usually at the level of the anterior iliac spine. Following retroperitoneal dissection, the border between the psoas and iliacus muscles was identified. The superior area of the SIJ was reached by spreading the muscles apart. The femoral nerve is identified and held laterally. The operation microscope was introduced and the joint capsule incised. Using a drill, the joint cartilage and adjacent bone were removed on both sides creating a groove around 6-7 mm wide, 20-22mm long and 20-21 mm deep. Bond graft from the iliac crest was formed to fit into the grove and inserted, after which the arthrodesis was fixed by a square plate with two screws on each side of the groove.

Example of posterior surgery, using an anterior approach (Smith et al.[44]*)*

A longitudinal incision is made cantered over the posterior-superior iliac spin and deepened to expose the bone. Retractors are used to pull back the soft tissue and expose the posterior portion of the inferior SIJ. An osteotome is used to remove the position of the posterior iliac crest that overhands the SI join and the bone is morselized to later use as a graft. Curettes and rongeurs are used to remove the cartilage from the articular portion of the joint and interosseous ligament from fibrous portion of the SI joint. One or two holes to accommodate cages are drilled into the SIJ joint and enlarger with a reamer. The cages are packed with morselized bone and placed into position under fluoroscopic guidance. Additional bone material is then packed in the remining open parts of the SIJ joint. Under fluoroscopic guidance, pins are placed from lateral to medial across the ilium, across the SI join and into the sacrum. EMG stimulation is typically used throughout the procedure to ensure safe placement of instrumentation.

Section C: Appendix B – Interview Topic Guides and summary of responses

Please refer to the following files attached as a part of the economic evidence submission:

Questions for Clinical Experts – Non-surgical.docx

Questions for Clinical Experts: Pain Mgt. consultants

Background

The sequence of questions below aim to inform an economic model comparing the cost of treating patients with chronic severe SIJ pain with a surgical intervention to non-surgical intervention from an NHS England perspective.
To populate the model, data are required on resource utilisation in alternative non-surgical treatment pathways for chronic severe SIJ pain. This includes data on how many sessions or procedures patients typically attend for in a six month or annual period, and how long patients are on treatment for.

Conservative management / Physical therapy

1. If patients are referred for physical therapy to treat chronic severe SIJ pain, how many physical therapy sessions do they typically attend over a six-month period?

2. Amongst patients that report their symptoms have improved after six months, **what percentage** are likely to then **stop treatment?**

3. Amongst patients that continue to report severe pain after six months of physical therapy, **what percentage** are then likely to then **stop treatment?** (either by patient choice or lack of funding)

4. Amongst the patients that continue to have on-going physical therapy (beyond 6 months), **what percentage** discontinue each year thereafter?

   For example, if 100 patients continued treatment beyond 6 months, how many are likely to stop treatment after 1 year, 1.5 years, 2 years etc.

Steroid Injections

5. If patients are referred for steroid injections to treat SIJ pain, how many procedures do they typically attend per year?

6. Amongst patients that report that their symptoms improve from severe to mild pain after six months, **what percentage** are likely to then **stop treatment** with steroid injections**?**

7. Amongst patients that still have severe pain or severe pain has return after six months, **what percentage** are then likely to **stop treatment?** (either by patient choice or lack of funding)

8. Amongst the patients that continue to have on-going steroid injections, (beyond 6 months), **what percentage** are likely to stop treatment at a later time point?

   For example, if 100 patients continued treatment beyond 6 months, how many are likely to stop treatment after 1 year, 1.5 years, 2 years etc.

Questions on RF Ablation

9. If patients are referred for regular RF Ablation to treat severe chronic SIJ pain, how many procedures are they likely to have per year?

10. Amongst patients that report that their symptoms have improved from severe to mild pain after six months, **what percentage** are then likely to **stop further treatment?**

11. Amongst patients that still have severe after six month, **what percentage** are then likely to **stop further treatment?**

12. Amongst patients that continue to have on-going RF Ablation, (beyond 6 months), **what percentage discontinue bi-annually**. For example, if 100 continued beyond 6 months, how many are likely to stop treatment after 1 year, 1.5 years, 2 years etc.

Questions on stepped treatment pathway

13. In what sequence are patients likely to be referred for the following non-surgical treatment options for chronic severe SIJ pain: Physical therapy, steroid injections and RF Ablation?

14. After every 6-months period on treatment with physical therapy/the first treatment specified, what percentage are likely to:
    a. Stop all treatments
    b. Switch to a steroid injections / second-line treatment
15. After every 6-months period on treatment with steroid injection/ the second-line treatment specified, what percentage are likely to:
    a. Stop all treatments
    b. Switch to a third treatment
16. After every 6-months period on treatment with RF Ablation or the second-line treatment specified, what percentage are likely to:
    a. Stop all treatments (either because the treatment has worked, or as no longer wish to seek treatment)

Data Collection

17. Are patient level data available reporting the average length of time patients are on any continuous non-surgical treatments?

18. If not, would it be feasible to start collecting this data as part of a registry?

Questions for Clinical Experts – Surgical.docx

Questions for Clinical Experts: Surgical Consultants

Background

The sequence of questions below aim to inform an economic model comparing the cost of treating patients with chronic severe SIJ pain with minimally invasive surgery (MIS) with iFuse to open surgery.
To populate the model, data are required on resource utilisation for MIS and surgery and open surgery. This requires assumptions on the main types of open surgery procedures provided to treat SIJ pain and the resource use implications.

Background information

Consultant Name:
Hospital:

Types of open surgery

- Prior to offering MIS with iFuse what were the main types of open surgical procedures you performed to treat SIJ pain:
    a) Please describe in terms of approach (e.g. anterior / posterior) and surgical consumables used
- What was the breakdown in terms of:
    a) anterior / posterior
    b) Unilateral / Bilateral
- Would all of the patients undergoing open surgery using the approaches discussed above have been candidates of MIS surgery with iFuse?
    a) If no, what proportion would have been candidates for MIS with iFuse and which surgical approaches could be displaced?

Surgical consumable costs

- We propose using the following assumptions to calculate the surgical consumable costs of open surgery. Are these assumptions and unit costs similar to the costs incurred by your hospital?

	Consumables	**Unit cost**	**Range**
Open – anterior	2 x Plates	**Still outstanding**	
	8 x screws		
	1 x graft material: (Either 2cm or 10 cm)	£350 for 2.5cc £650 for 10 cc	

	Consumables	**Unit cost**	**Range**
Open – posterior	2 x pedicle screws	£800	£600 - £1200
	1 x cross connecting rod	£250	£200 - £300
	1 x PLIF cages	£900	£700 - £1100
	1 X BMB sponge (Either 2cm or 10 cm and % using skin autograph)	£1200	£900 - £1100
	2 x screw caps, nuts etc.	£150	£120 - £180
	Total	**£4100**	**£3,120 - £3980**

	Consumables	**Unit cost**
MIJ iFuse	3 x surgical Implants	3 * £1155
	Set of surgical consumables	1 x £275
	3 x steinmann pins	3 * £47
	1 x exchange pin	1 * £47
	1 x drill	1 x 131.00
	Total	**£4,059**

- If not, how do the costs differ?

Surgical Times

Open surgery

- What is the average length and range (max and min) of an open surgical procedure (time in theatre) by:
    - Anterior unilateral
    - Anterior bilateral
    - Posterior unilateral
    - Posterior bilateral
- Do surgical times vary by patient demographics and if yes please describe how?

MIS iFuse

- What is the average length and range of an MIS with iFuse procedure (time in theatre) by:
    - Unilateral
    - Bilateral
- Do surgical times vary by patient demographics and if yes please describe how?

Length of hospital stay

Open surgery

- What is the average length of hospital stay (time from admission to discharge) and range (max and min) amongst patients who have had an open surgical procedure to treat SIJ pain by:
    - Anterior unilateral
    - Anterior bilateral
    - Posterior unilateral
    - Posterior bilateral
- Do recovery times vary by patient demographics and if yes please describe how?

MIS iFuse

- What is the average length of hospital stay (time from admission to discharge) amongst patients who have had an MIS with iFuse procedure to treat SIJ pain by:
    - Unilateral
    - Bilateral
- Do recovery times vary by patient demographics and if yes please describe how

Assessment & Follow-up

For surgical procedures, what is the standard pathway for pre-surgical assessment and follow-up:

Pre-surgery:

- Number of consultations? For Open / MIS iFuse
- Are these consultant-led, nurse led or multidisciplinary? For Open / MIS iFuse

Follow-up in first 6 months

- Number of consultations? For Open / MIS iFuse
- Are these consultant-led, nurse-led or multidisciplinary? For Open / MIS iFuse

Follow-up beyond 6 months

- Number of consultations? For Open / MIS iFuse
- Are these consultant-led, nurse-led or multidisciplinary? For Open / MIS iFuse

Surgical Revisions

Open

- In your experience, what percentage of patients who have had open surgery to treat SIJ pain will have a surgical revision within 5 years follow-up?

iFuse

- In your experience, what percentage of patients who have had MIS iFuse surgery to treat SIJ pain will have a surgical revision within 5 years follow-up?

Both

- How do revision surgeries differ from the original procedure in terms of:
    a) equipment use
    b) theatre time
    c) length of stay?

Medication Costs

- What pain medication are patients typically on prior to undergoing surgery to treat SIJ pain? Please describe the drug and dose

- What percentage of patients continue to require medication after:
    a) An open surgical procedure?
    b) MIS with iFuse?

- Amongst those that continue to require pain medication after surgery, does the prescription differ compared to pre-surgery? If yes, please describe how

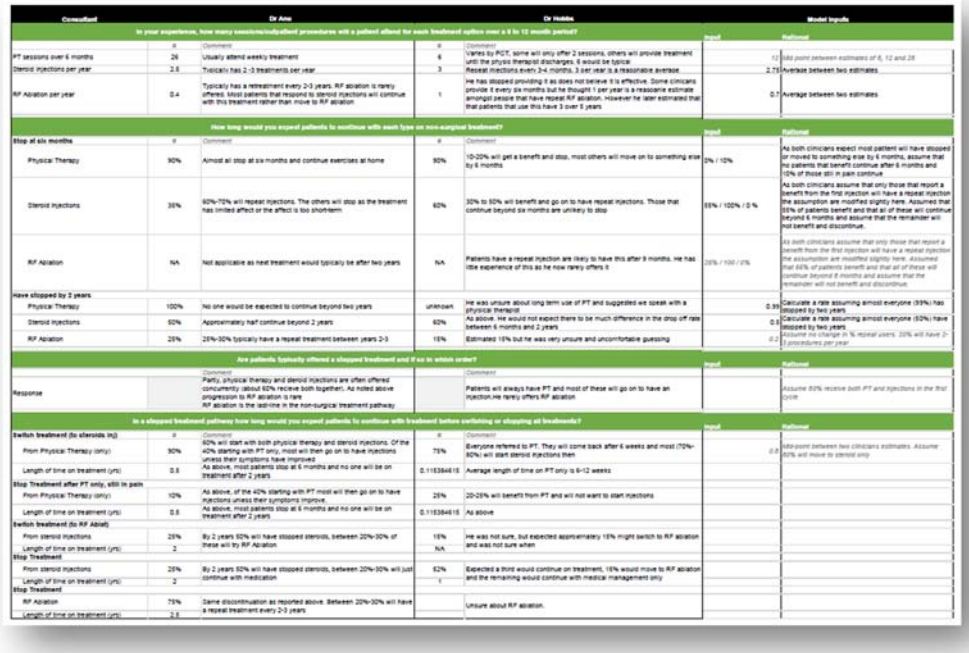
Data Collection

- Are patient level data reporting consumable costs, surgical times and length of hospital stay with open surgery or MIS with iFuse to treat SIJ pain collected in your hospital?

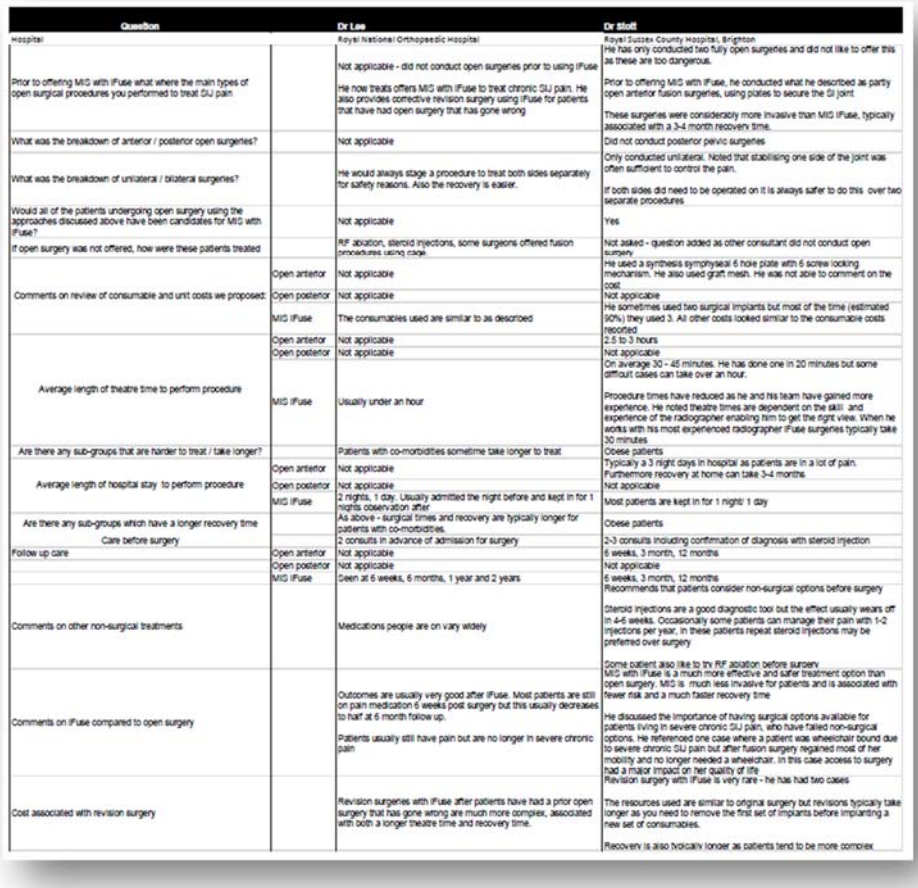
If yes, are you able to share this data with Si-bone to support a submission to NICE

SI-BONE KoLs Interview Responses.xlsx

See Images below and attachment.



Consultant	Dr Ano		Dr Hobbs		Model Inputs	
In your experience, how many sessions/visits/allied procedures will a patient attend for each treatment option over a 6 to 12 month period?					Input	Rationale
	#	Comment	#	Comment		
PT sessions over 6 months	26	Usually attend weekly treatment	6	Varies by PCT, some will only offer 2 sessions, others will provide treatment until the physio therapist discharges. 6 would be typical	12	Mid point between estimates of 6, 12 and 26
Steroid injections per year	2.5	Typically has 2 -3 treatments per year.	3	Repeat injections every 3-4 months, 3 per year is a reasonable average.	2.75	Average between two estimates
RF Ablation per year	0.4	Typically has a retreatment every 2-3 years. RF ablation is rarely offered. Most patients that respond to steroid injections will continue with this treatment rather than move to RF ablation	1	He has stopped providing it as does not believe it is effective. Some clinicans provide it every six months but he thought 1 per year is a reasoanle estimate amongst people that have repeat RF ablation. However he later estimated that that patients that use this have 3 over 5 years	0.7	Average between two estimates
How long would you expect patients to continue with each type on non-surgical treatment?					Input	Rationale
Stop at six months	#	Comment	#	Comment		
Physical Therapy	90%	Almost all stop at six months and continue exercises at home	90%	10-20% will get a benefit and stop, most others will move on to something else by 6 months	5% / 10%	As both clinicians expect most patient will have stopped or moved to something else by 6 months, assume that no patients that benefit continue after 6 months and 10% of those still in pain continue
Steroid Injections	35%	60%-70% will repeat injections. The others will stop as the treatment has limited affect or the affect is too short-term	60%	30% to 50% will benefit and go on to have repeat injections. Those that continue beyond six months are unlikely to stop	65% / 100% / 0 %	As both clinicians assume that only those that report a benefit from the first injection will have a repeat injection the assumption are modified slightly here. Assumed that 65% of patients benefit and that all of these will continue beyond 6 months and assume that the remainder will not benefit and discontinue.
RF Ablation	NA	Not applicable as next treatment would typically be after two years	NA	Patients have a repeat injection are likely to have this after 9 months. He has little experience of this as he now rarely offers it	35% / 100 / 0%	*As both clinicians assume that only those that report a benefit from the first injection will have a repeat injection the assumption are modified slightly here. Assumed that 65% of patients benefit and that all of these will continue beyond 6 months and assume that the remainder will not benefit and discontinue.*
Have stopped by 2 years						
Physical Therapy	100%	No one would be expected to continue beyond two years	unknown	He was unsure about long term use of PT and suggested we speak with a physical therapist	0.99	Calculate a rate assuming almost everyone (99%) has stopped by two years
Steroid Injections	50%	Approximately half continue beyond 2 years	40%	As above, he would not expect there to be much difference in the drop off rate between 6 months and 2 years	0.5	Calculate a rate assuming almost everyone (50%) have stopped by two years
RF Ablation	25%	25%-30% typically have a repeat treatment between years 2-3	15%	Estimated 15% but he was very unsure and uncomfortable guessing	0.2	*Assume no change in % repeat years. 20% will have 2-3 procedures per year*
Are patients typically offered a stepped treatment and if so in which order?					Input	Rationale
		Comment		Comment		
Response		Partly, physical therapy and steroid injections are often offered concurrently (about 60% receive both together). As noted above progression to RF ablation is rare RF ablation is the last-line in the non-surgical treatment pathway		Patients will always have PT and most of these will go on to have an injection.He rarely offers RF ablation		*Assume 60% receive both PT and injections in the first cycle*
In a stepped treatment pathway how long would you expect patients to continue with treatment before switching or stopping at treatments?					Input	Rationale
Switch treatment (to steroids inj)	#	Comment	#	Comment		
From Physical Therapy (only)	90%	60% will start with both physical therapy and steroid injections. Of the 40% starting with PT only, most will then go on to have injections unless their symptoms have improved	75%	Everyone referred to PT. They will come back after 6 weeks and most (70%-80%) will start steroid injections then	0.8	*Mid-point between two clinicians estimates. Assume 80% will move to steroid only*
Length of time on treatment (yrs)	0.5	As above, most patients stop at 6 months and no one will be on treatment after 2 years	0.115384615	Average length of time on PT only is 6-12 weeks		
Stop Treatment after PT only, still in pain						
From Physical Therapy (only)	10%	As above, of the 40% starting with PT most will then go on to have injections unless their symptoms improve.	25%	20-25% will benefit from PT and will not want to start injections		
Length of time on treatment (yrs)	0.5	As above, most patients stop at 6 months and no one will be on treatment after 2 years	0.115384615	As above		
Switch treatment (to RF Ablat)						
From steroid injections	25%	By 2 years 50% will have stopped steroids, between 20%-30% of these will try RF Ablation	15%	He was not sure, but expected approximately 15% might switch to RF ablation and was not sure when		
Length of time on treatment (yrs)	2		NA			
Stop Treatment						
From steroid injections	25%	By 2 years 50% will have stopped steroids, between 20%-30% will just continue with medication	52%	Expected a third would continue on treatment, 15% would move to RF ablation and the remaining would continue with medical management only		
Length of time on treatment (yrs)	2		1			
Stop Treatment						
RF Ablation	75%	Same discontinuation as reported above. Between 20%-30% will have a repeat treatment every 2-3 years		Unsure about RF ablation.		
Length of time on treatment (yrs)	2.5					



Question		Dr Lee	Dr Stott
Hospital		Royal National Orthopaedic Hospital	Royal Sussex County Hospital, Brighton
Prior to offering MIS with iFuse what where the main types of open surgical procedures you performed to treat SIJ pain		Not applicable - did not conduct open surgeries prior to using iFuse He now treats offers MIS with iFuse to treat chronic SIJ pain. He also provides corrective revision surgery using iFuse for patients that have had open surgery that has gone wrong	He has only conducted two fully open surgeries and did not like to offer this as these are too dangerous. Prior to offering MIS with iFuse, he conducted what he described as partly open anterior fusion surgeries, using plates to secure the SI joint These surgeries were considerably more invasive than MIS iFuse, typically associated with a 3-4 month recovery time.
What was the breakdown of anterior / posterior open surgeries?		Not applicable	Did not conduct posterior pelvic surgeries
What was the breakdown of unilateral / bilateral surgeries?		He would always stage a procedure to treat both sides separately for safety reasons. Also the recovery is easier.	Only conducted unilateral. Noted that stabilising one side of the joint was often sufficient to control the pain. If both sides did need to be operated on it is always safer to do this over two separate procedures
Would all of the patients undergoing open surgery using the approaches discussed above have been candidates for MIS with iFuse?		Not applicable	Yes
If open surgery was not offered, how were these patients treated		RF ablation, steroid injections, some surgeons offered fusion procedures using cage.	Not asked - question added as other consultant did not conduct open surgery
Comments on review of consumable and unit costs we proposed:	Open anterior	Not applicable	He used a synthesis symphyseal 6 hole plate with 6 screw locking mechanism. He also used graft mesh. He was not able to comment on the cost
	Open posterior	Not applicable	Not applicable
	MIS iFuse	The consumables used are similar to as described	He sometimes used two surgical implants but most of the time (estimated 90%) they used 3. All other costs looked similar to the consumable costs recorded
Average length of theatre time to perform procedure	Open anterior	Not applicable	2.5 to 3 hours
	Open posterior	Not applicable	Not applicable
	MIS iFuse	Usually under an hour	On average 30 - 45 minutes. He has done one in 20 minutes but some difficult cases can take over an hour. Procedure times have reduced as he and his team have gained more experience. He noted theatre times are dependent on the skill and experience of the radiographer enabling him to get the right view. When he works with his most experienced radiographer iFuse surgeries typically take 30 minutes
Are there any sub-groups that are harder to treat / take longer?		Patients with co-morbidities sometime take longer to treat	Obese patients
Average length of hospital stay to perform procedure	Open anterior	Not applicable	Typically a 3 night days in hospital as patients are in a lot of pain. Furthermore recovery at home can take 3-4 months
	Open posterior	Not applicable	Not applicable
	MIS iFuse	2 nights, 1 day. Usually admitted the night before and kept in for 1 nights observation after	Most patients are kept in for 1 night/ 1 day
Are there any sub-groups which have a longer recovery time		As above - surgical times and recovery are typically longer for patients with co-morbidities.	Obese patients
Care before surgery		2 consults in advance of admission for surgery	2-3 consults including confirmation of diagnosis with steroid injection
Follow up care	Open anterior	Not applicable	6 weeks, 3 month, 12 months
	Open posterior	Not applicable	Not applicable
	MIS iFuse	Seen at 6 weeks, 6 months, 1 year and 2 years	6 weeks, 3 month, 12 months
Comments on other non-surgical treatments		Medications people are on vary widely	Recommends that patients consider non-surgical options before surgery Steroid injections are a good diagnostic tool but the effect usually wears off in 4-6 weeks. Occasionally some patients can manage their pain with 1-2 injections per year, in these patients repeat steroid injections may be preferred over surgery Some patient also like to try RF ablation before surgery
Comments on iFuse compared to open surgery		Outcomes are usually very good after iFuse. Most patients are still on pain medication 6 weeks post surgery but this usually decreases to half at 6 month follow up. Patients usually still have pain but are no longer in severe chronic pain	MIS with iFuse is a much more effective and safer treatment option than open surgery. MIS is much less invasive for patients and is associated with fewer risk and a much faster recovery time He discussed the importance of having surgical options available for patients living in severe chronic SIJ pain, who have failed non-surgical options. He referenced one case where a patient was wheelchair bound due to severe chronic SIJ pain but after fusion surgery regained most of her mobility and no longer needed a wheelchair. In this case access to surgery had a major impact on her quality of life
Cost associated with revision surgery		Revision surgeries with iFuse after patients have had a prior open surgery that has gone wrong are much more complex, associated with both a longer theatre time and recovery time.	Revision surgery with iFuse is very rare - he has had two cases The resources used are similar to original surgery but revisions typically take longer as you need to remove the first set of implants before implanting a new set of consumables. Recovery is also typically longer as patients tend to be more complex

In addition to conducting interviews we asked surgeons by email to provide estimates for the cost of consumables used to perform open surgery

Question: Please provide an estimate of the consumable costs associated with anterior fusion surgery
Consultant: Peter Giannoudis, Trauma & Orthopaedic Surgery, School of Medicine, University of Leeds

Response
2 plates and 8 screws = £500
1 cannulated screw with washer= £100
2 hours of theatre: 120 X 38 = £4520
1 drain=£60
1 DBM= £500
Stiches X 3= £60

We also asked the Si-Bone sales team to consult with hospital staff to provide a range of estimates for the consumable costs listed in different papers describing open fusion surgeries. The estimates provided are listed

	Low	Med	High
Open surgical approach described in Wise and Dall, 2008	£	£	£
Two threaded fusion cages (Medtronic	2000	2000	2000
BMP Sponge	900	1200	1600
Total	**2900**	**3200**	**3600**
Open surgical approach ddescribed in Arnold Graham Smoth spine across the sea abstract			
Two pedicle screws	600	800	1200
One cross connecting rod	200	250	300
One PLIF cage	700	900	1100
One BMB sponge	900	1200	1600
Two screw caps, nuts, etc.	120	150	180
Total	2520	3300	4380
Open surgical technique for PLIF Cages - Smith 2013			
Two PLIF Cages	1400	1800	2200
BMP Sponge	700	900	1100
Two 6.5 mm cancellous lag screws with washers	100	140	200
Total	2200	2840	3500

Full References

Smith, A. G. "Arthrodesis of the Sacroiliac Joint Using Pedicle Screw Fixation and Bone Morphogenetic Protein for Chronic Sprain Causing Disabling Pain" Spine Across the Sea. July 2009. Maui, Hawaii

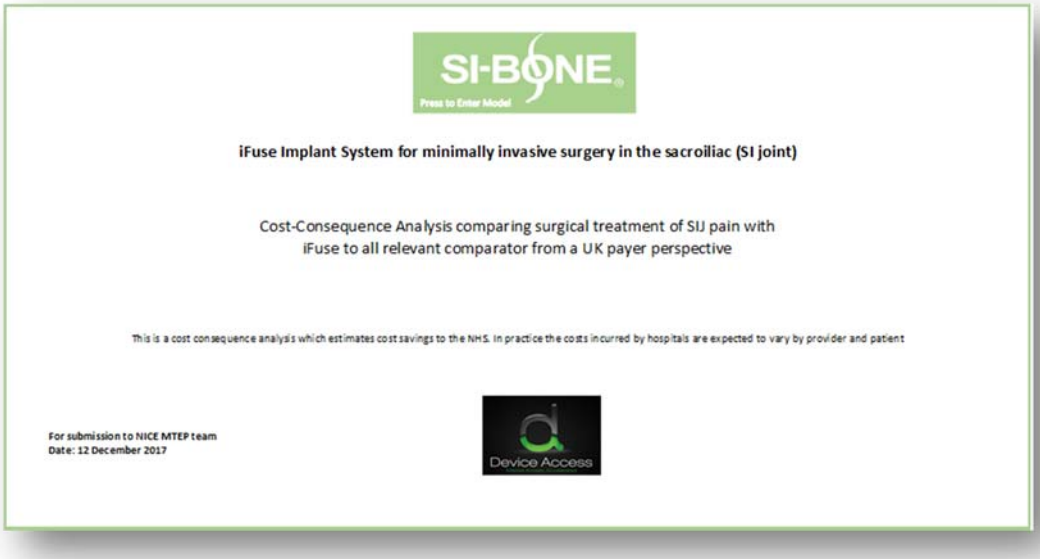
Smith, Arnold Graham, et al. "Open versus minimally invasive sacroiliac joint fusion: a multi-center comparison of perioperative measures and clinical outcomes." Annals of surgical innovation and research 7.1 (2013): 14.

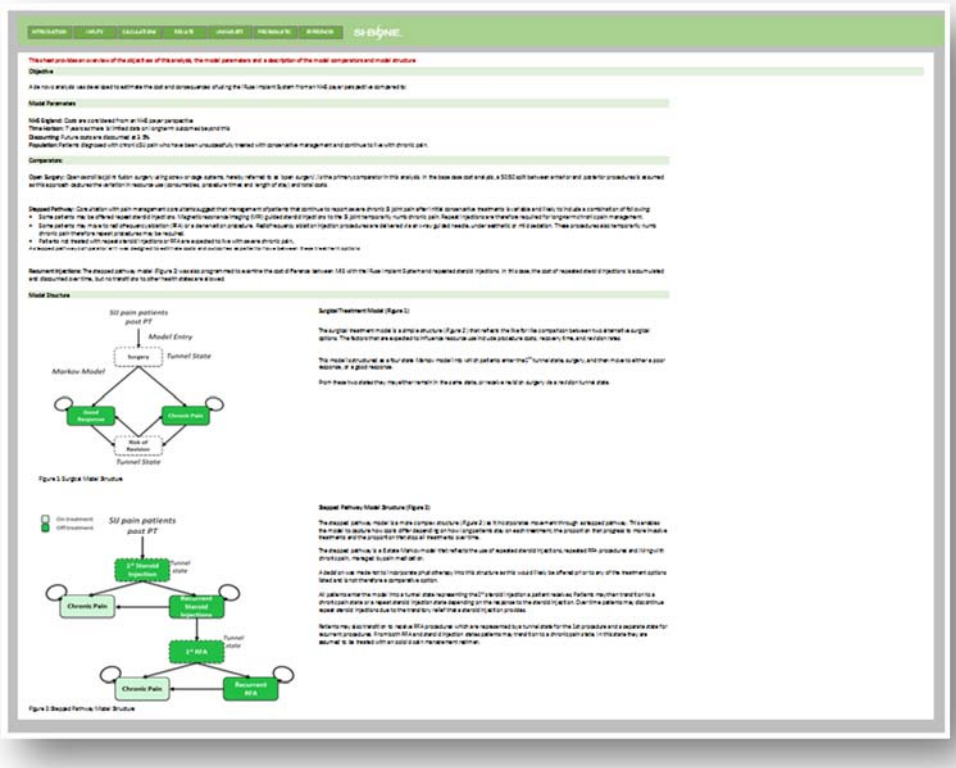
Wise, C. L., Dall, B. E. "Minimally Invasive Sacroiliac Arthrodesis. Outcomes of a New Technique" *J Spinal Disord Tech. (2008) 21.8*

Section C: Appendix C – Economic Model

Please refer to the following file attached as a part of the economic evidence submission:

1. SiBone_MTEP Model 20171212.xlsm





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Please use a recognised referencing style, such as Harvard or Vancouver.

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10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (Sec. 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

The Cochrane Library.

Response

10.1.2 The date on which the search was conducted.

Response

10.1.3 The date span of the search.

Response

10.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Response

10.1.6 The inclusion and exclusion criteria.

Response

10.1.7 The data abstraction strategy.

Response

10.2 Appendix 2: Search strategy for adverse events (Sec. 7.7.1)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

The Cochrane Library.

Response

10.2.2 The date on which the search was conducted.

Response

10.2.3 The date span of the search.

Response

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

10.2.6 The inclusion and exclusion criteria.

Response

10.2.7 The data abstraction strategy.

Response

10.3 Appendix 3: Search strategy for economic evidence (Sec 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT

NHS EED.

Response

10.3.2 The date on which the search was conducted.

Response

10.3.3 The date span of the search.

Response

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

10.4 Appendix 4: Resource identification, measurement and valuation (Sec 9.3.2)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED

EconLIT.

Response

10.4.2 The date on which the search was conducted.

Response

10.4.3 The date span of the search.

Response

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

10.4.6 The inclusion and exclusion criteria.

Response

10.4.7 The data abstraction strategy.

Response

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

National Institute for Health and Care Excellence

Topic Briefing

Collated comments – responses from questionnaires

External adviser comments on MT355 iFuse implant system for chronic sacroiliac joint pain

Expert adviser details and declarations of interest:

Expert adviser #1	Mr Mark Thomas, Consultant Orthopaedic and Spinal Surgeon, Frimley Health NHS Foundation Trust
	DOI: Yes, I teach on Sacroiliac Joint anatomy and surgical treatment courses once or twice a year. These courses are run by SIbone (a company that produces implants for SI joint fusion) and I receive an hourly fee for lecturing as well as travel expenses.
Expert adviser #2	Mrs Elaine Buchanan, Spinal Consultant Physiotherapist, Oxford University NHS Foundation Trust
	DOI: None
Expert adviser #3	Mr Robert Lee, Consultant Orthopaedic and Spinal Surgeon, Royal National Orthopaedic Hospital NHS Trust
	DOI: Consultant of SI-Bone (manufacturer of iFuse) along with a number of spinal companies. Has expressed a clear view via the Daily Mail regarding a good result in surgery for one of Mr Lee's patients. A spinal company (not Si-Bone) sponsors a fellow Mr Lee works with and are both participating in company sponsored trials at RNOH. No trials involve Si-Bone.
Expert adviser #4	Mr David Chapple, Trauma and Orthopaedic Surgeon, Salisbury NHS Trust
	DOI: None
Expert adviser #5	Mr Hilali Noordeen, Consultant Spinal Surgeon, Royal National Orthopaedic Hospital NHS Trust
	DOI: Consultation to K2M & Ellipse Technologies. Royalties from K2M technology.
Expert adviser #6	Mr Bronek Boszczyk, Consultant Spinal Surgeon and Head of Service, University of Nottingham
	DOI: SI bone is one of many sponsors of educational courses that I run. See www.nspine.com

Expert adviser comments received

1	Please describe your level of experience with the technology, for example: − Are you familiar with the technology? − Have you used it? − Are you currently using it? − Have you been involved in any research or development on this technology? − Do you know how widely used this technology is in the NHS?	EA#1: − I am very familiar with this technology and have been performing this surgery for over 4 years now. To date I have performed nearly 40 cases. − I have been involved with the company (SI Bone) in the development of the second generation instrumentation and teach on instructional courses that are put on by the company to teach surgeons about sacroiliac joint disease and the technique of minimally invasive joint fusion. − My understanding is that at present the technique is not widely used in the NHS although it is becoming more popular. Sacroiliac joint dysfunction requiring surgery is relatively uncommon and so the majority of surgeons who have donr the procedure have not done a large number of cases.
		EA#2 − I am not familiar with this specific technology. I am however familiar with sacral instrumentation. − I do not perform any form of surgery − I have not been involved in any research/development on this technology − I have no knowledge of the use of this technology in the UK health and social care system
		EA#3 − I am familiar with the technology and have performed SIJ Fusions since 2013. − I still currently perform SIJ Fusions − I have not been involved in the research or development of the technology − The technology is used by a limited number of surgeons mainly due to the technical expertise required in performing the procedure. But the surgeons who perform these operations do a considerable volume.
		EA#4 − Yes − Yes − Yes − No − Used in a few centres that undertake spinal surgery. Usually only the orthopaedic spinal teams

		EA#5 – Yes – No – No – No – Not used at present
		EA#6 – Have used in several cases – Have not been approached for R&D for this implant – Sporadic use in NHS – mainly due to limitations in training
2	Has the technology been superseded or replaced?	EA#1 No
		EA#2 I have no knowledge to inform this response
		EA#3 SIJ Fusion technology is more minimally invasive than 15-20 years ago The use of computer navigation technology to perform the operation greatly reduces the risk of complications
		EA#4 Current
		EA#5 No

		EA#6 This is the current technology – it is an improvement on old open techniques. There are several competitor products with a lesser publication track-record

Current management

3	How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?	EA#1 Percutaneous stabilisation of the SI joint for trauma has been performed for many years using canulated screws. Fusion surgery for degenerative conditions or instability was standardly performed open. This technique adapts the percutaneous approach to achieve stabilization / fusion so removing the need for open surgery.
		EA#2 I have no knowledge to inform this response
		EA#3 The iFuse technology is a variation on the many types of minimally invasive fusion technology available. They all rely on the accurate placement of guidewires into the sacrum and use 2-3 bolts/cages. The iFuse cage is not a screw but a titanium cage which allows bony ongrowth and resists rotation. It is more of a novel design rather than a dramatic change in the way we perform minimally invasive SIJ fusions.
		EA#4 It is innovative as it uses a percutaneous guided preparation and placement of the implants rather than n open approach. I usual does not require any bone graft
		EA#5 It is a novel design for an intractable(?) problem

		EA#6 It is a significant improvement as it provides immediate stability without needing to wait for bony through growth which is the case with the more traditional techniques. SI-Bone consist of Titanium spacers which allow bone to attach to the surface rather than rely on bone growing all the way through the implant across the joint.
4	Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?	EA#1 Following the success of iFuse, there have been many competing products launched. To my knowledge these all vary in that they use screws across the joint rather than the triangular implants but all utilise the percutaneous technique.
		EA#2 I have no knowledge to inform this response
		EA#3 The ones listed in the topic briefing are all competing technologies. The majority work in the same way with screws/cages across the joint. However RIALTO and DIANA cages are placed in different ways and are inserted along the joint line rather than across the joint.
		EA#4 Yes. Usually open posterior approaches with bone graft required
		EA#5 No
		EA#6 Several large manufacturers have come up with competitor devices. To my knowledge there are no direct comparison studies to show superiority of one system over the other. An extensive overview can be found under: www.thespinemarketgroup.com and search for SI joint

Potential patient benefits

5	What do you consider to be the potential benefits to patients from using this technology?	EA#1 MIS surgery. Short hospital stay (overnight). Short operative time with minimal blood loss. Straight forward technique with very low complication rate.
		EA#2 I have no knowledge to inform this response
		EA#3 iFuse appears to have the best data available looking at the outcomes and although this data is not long term data, the results are extremely positive. The benefits are shorter length of stay, faster recovery and rehabilitation and less complications.
		EA#4 Less collateral injury, safer approach, shorter hospital stay, fewer complications.
		EA#5 Pain relief from sacro(?) – I have patients(?) unresponsive to conservative treatment.
		EA#6 In comparison to the traditional open techniques quicker mobilisation and a lower failure rate.
6	Are there any groups of people who would particularly benefit from this technology?	EA#1 Any patient who has sacroiliac joint pain that is resistant to non operative management
		EA#2 −Those with radiological evidence of sacroiliac disorders with concordant clinical symptoms, who have not responded to an optimal pathway of conservative care, sacor-iliac injection or radiofrequency ablation.

		EA#3 All patients who have been diagnosed with SIJ pain who are suitable for SIJ fusions. All patients must follow the NASS guidelines for SIJ fusion – namely positive history and clinical examination, positive response to an injection and failed conservative management.
		EA#4 Post spinal fusion patients with ongoing sacro iliac pain and primary sacroiliac joint arthritic patients.
		EA#5 See above
		EA#6 Patients with posttraumatic SI joint arthritis and patients with rheumatoid (non-infective) sacroiliitis
7	Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	EA#1 Yes – as stated above. The patient pathway is much simpler and quicker.
		EA#2 −The clinical threshold for instrumentation should be unchanged. −The technology will likely be an alternative way of instrumenting patients who need instrumentation. −I am not aware of any robust evidence that it will improve outcome.
		EA#3 There are other minimally invasive procedures which are shown in the topic briefing. However as mentioned above, the data for iFuse is impressive. These improved outcomes would lead to less hospital visits and less burden on pain management and less revision surgery.
		EA#4 Potential shorter stays and less complications

		EA#5 Yes on all counts. SIJ pain is a difficult problem.
		EA#6 Hopefully fewer revisions than conventional techniques and with the right patient selection quicker recovery

Potential system impact

8	What do you consider to be the potential benefits to the health or care system from using this technology?	EA#1 Covered above in short operative time and hospital stay but also results suggest that this is an effective treatment for a difficult and disabling condition so the treatment will reduce the burden on the health sector as a whole in the long term.
		EA#2 −Potentially cost, shorter procedure time, length of stay, morbidity, speed of recovery, and clinically meaningful functional outcomes.
		EA#3 Better outcomes with less revision surgery will lead to less strain on financial resources in the NHS as well as allowing return to work. Financial implications also include less use of analgesia and less hospital visits
		EA#4 Treatment for a group of patients that other treatments have a limited success
		EA#5 (1) Less hospital visits (2) Longer working life
		EA#6 Quicker return to work and potentially lower cost as no additional fusion material required.

9	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?	EA#1 I would see it costing less over the whole pathway as the patient should be able to return much quicker to their pre morbid state.
		EA#2 I have no knowledge to inform this response
		EA#3 I would agree with the topic briefing in that the technology in the long term will cost less than current standard care.
		EA#4 More than no treatment a but less than current fusion operations
		EA#5 More than current care. Currently injections or denervation (repeated) is the standard of care.
		EA#6 Should ideally cost less.
10	What do you consider to be the resource impact from adopting this technology? Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?	EA#1 The only impact over open surgery is a shorter stay and quicker surgery times. I do not feel that this technique could be performed safely in primary care as it is still an invasive surgical procedure that requires the back up of a surgical centre.
		EA#2 I have no knowledge to inform this response
		EA#3 There are no resource implications unless the decision is made that these fusions should all be done under navigation.

		There is a potential risk of neurological injury when performing this procedure and I have personally seen two patients with devastating nerve injuries performed by other surgeons which are being pursued down the medicolegal path. In both these case 2D image intensifiers were used causing malposition of the cage. One was with Silex and the other case was with iFuse. However the malposition is implant independent – it is to do with recognition and deciphering the complex anatomy of the SI Joint. 3D computer navigation almost completely eliminates screw/implant malposition but this technology is available in only a few centres. If the decision is made that these fusions should only be done at these centres then it would have resource implications. From a personal perspective I refuse to do these operations without 3D navigation.
		EA#4 No great change in resource impact can be undertaken by the same staff
		EA#5 Simply an increase cost base
		EA#6 None
11	Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?	EA#1 The surgeon must be trained in the surgical approach and technique.
		EA#2 I have no knowledge to inform this response
		EA#3 Please see point 10. Otherwise no changes. Only surgeon training required.
		EA#4 Specific training required, rest of the resourses are similar to performing other spinal surgical procedures.

		EA#5 Yes, training & systems using product
		EA#6 None except for surgeon training
12	Are you aware of any safety concerns or regulatory issues surrounding this technology?	EA#1 No
		EA#2 I have no knowledge to inform this response
		EA#3 No specific concerns. The concerns regarding implant malposition and nerve injury apply to all SIJ fusion technologies.
		EA#4 Known
		EA#5 No
		EA#6 None

General advice

13	Please add any further comments on your particular experiences or knowledge of the	EA#1 I have had no difficulty in introducing this in either my NHS or private hospital

	technology, or experiences within your organisation.	EA#2 −It would be appropriate for a pathway of care to be developed and agreed.
		EA#3 Once again, referring to point 10, there is a potential for nerve injury which I have seen twice so far in other surgeon's patients. This is due to malposition under normal x-ray guidance. I personally feel that due to variations in anatomy and at times difficulty in obtaining proper intraoperative images, these should only be done under 3D navigation. My experience at RNOH has been very positive and have not had to revise any of the patients I have operated on. I also believe that SIJ pain is underdiagnosed and that there are many patients who can be helped by this technology.
		EA#4 The implants are too expensive at present and pressure should be applied to bring the cost down.
		EA#5 I think this is a (?) intervention for an (?) problem.
		EA#6 Have used for several cases and find this easier and more reliable than the traditional method.

Other considerations

14	Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population?	EA#1 Unknown
		EA#2 I have no knowledge to inform this response

		EA#3 This is hard to estimate. About 20% of back pain comes from the SI Joint. Of this 50-80% resolves with conservative management alone. The remainder would then be eligible for this intervention
		EA#4 Uk wide about ,250 to 500 per year
		EA#5 I would use it in my practice approximately once per year.
		EA#6 Could not say – at this time we do around 5 cases a year – this would probably rise when offered more readily and referers become aware.
15	Would this technology replace or be an addition to the current standard of care?	EA#1 It would replace the current open techniques
		EA#2 −Replace current methods of instrumentation
		EA#3 The current standard of care should be minimally invasive fusion. I consider open fusion to be quite a barbaric procedure that should never be done.
		EA#4 replace
		EA#5 An addition

		EA#6 Addition and replace older technology
16	Are there any issues with the usability or practical aspects of the technology?	EA#1 No
		EA#2 I have no knowledge to inform this response
		EA#3 Please see points 10 and 13
		EA#4 no
		EA#5 Appropriate training required
		EA#6 None
17	Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?	EA#1 No
		EA#2 I have no knowledge to inform this response
		EA#3 Please see points 10 and 13 Surgeons training is important not only from the technical perspective but also from the perspective of recognising SI Joint pain.

		EA#4 Cost of the implants to NHS
		EA#5 No
		EA#6 None
18	Are you aware of any further evidence for the technology that is not included in this briefing?	EA#1 No
		EA#2 −I have no knowledge to inform this response
		EA#3 No – the briefing is comprehensive
		EA#4 n/a
		EA#5 No
		EA#6 Not beyond what is already available
19	Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology?	EA#1 The users who collect their data on the British Spinal Registry will have outcome data but this data is also covered in a lot of the lesser trails

	Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.	EA#2 −I have no knowledge to inform this response
		EA#3 We are aiming to publish a paper on 3D navigation in SI Joint fusions using iFuse Am happy to share this with NICE once it is ready for submission
		EA#4 Local spinal centers and British Spine Registry collect data.
		EA#5 No
		EA#6 Only as part of the British Spine Registry
20	Is there any research that you feel would be needed to address uncertainties in the evidence base?	EA#1 No
		EA#2 Independent appropriately powered RCT's comparing i-fuse to: − conservative NHS care, with long-term outcomes including quality of life, functional ability and health care utilisation. − combined physical and psychological programme, with long-term outcomes including quality of life, functional ability and health care utilisation. − sacroiliac injection, with long-term outcomes including quality of life, functional ability and health care utilisation. − early i-fuse versus a NHS stepped approach to care, with long-term outcomes including quality of life, functional ability and health care utilisation. − currently used NHS instrumentation methods, with outcomes including cost, procedure time, length of stay, morbidity, speed of recovery, quality of life, functional ability and health care utilisation and need for revision.

		EA#3 No – I think the current trials are sufficient.
		EA#4 Multicentre trial for the use in post spinal fusion patients
		EA#5 No
		EA#6 None beyond what is already published
21	How useful would NICE guidance on this particular technology be to you or other NHS colleagues?	EA#1 It helps in ensuring that one's practice is sensible and that the procedures are recognised as being reasonable. Therefore one can justify their use in the annual appraisal andensure funding is approved.
		EA#2 Helpful, but we have a very low volume of patients who have sacro-iliac instrumentation for chronic sacroiliac joint pain.
		EA#3 NICE guidance has already been published on SI Joint Fusions. NICE approval of this MIS technology will help hospitals to allow this technology to be performed locally, as it will show that it has been well reviewed and recommended.
		EA#4 Very helpful
		EA#5 Very useful in the management of this SIJ dysfunction.

		EA#6 Useful for referring health care professionals

National Institute for Health and Care Excellence

External Assessment Centre correspondence

MT355 iFuse implant system for treating chronic sacroiliac joint pain

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
Clinical submission - Section 2.1	The company has mentioned iFuse and iFuse 3D? Does the submission pertain to iFuse only or both iFuse and iFuse 3D?	EAC's interpretation of answer following a teleconference with the manufacturer: The company listed all CE marked iFuse products and this included iFuse 3D. The submission pertains to iFuse and not iFuse 3D as the bulk of the evidence is for iFuse. It is the EAC's understanding that there is one in vivo (sheep) study for iFuse 3D and that this technology will not be considered in this submission. Added by the manufacturer: For completeness, the company included all SI-BONE products that are CE marked. The current MTEP submission is for the IFuse Implant System only and does not pertain to iFuse 3D.	None.
Clinical submission - Section 3.8	Is there a need for additional technology/infrastructure in order to plan where the iFuse implants should be placed? The EAC noted that it had seen OsiriX software being used during the planning stage.	EAC's interpretation of answer following a teleconference with the manufacturer: The company stated that there would be a need for a pre-operative evaluation, using some form of imaging (CT/MRI), to evaluate the lumbar spine and pelvis. This evaluation would rule out other causes of SI joint pain and ensure the area was free from infection or tumour. The imaging steps used during this evaluation could be used to determine where the implants should be placed. Added by the manufacturer: Use of pre-operative planning imaging software is not part of the typical iFuse procedure. Pre-operative planning with special software was not and is not considered necessary or recommended prior to performing an iFuse procedure. As part of the routine diagnostic evaluation of patients with SI joint pain, patients will typically undergo cross sectional imaging of the pelvis. This imaging (CT scan or MRI) is performed to rule out infection or tumor in the area of the SI joint and to rule out hip pathology. This cross-sectional study of the pelvis (CT scan or MRI) will	None.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
		allow the surgeon to assess the anatomy of the sacrum and Si joint. Optimal implant placement can be determined/planned using this imaging study. No specialty software is needed. No additional investment or resources will be necessary.	
Clinical submission - Section 3.8	[Question from Paul Dimmock (NICE lead analyst)] – A clinical expert has commented that there is a potential for nerve injury due to malposition of iFuse implants under normal (2D) x-ray guidance and he feels that due to variations in anatomy and occasional difficulty in obtaining proper intraoperative images, iFuse implants should only be inserted under 3D navigation (which would require specialised operating theatre equipment). Could the company comment on this point please?	Manufacturer's response The iFuse Implant System received both FDA clearance (2008) and CE Mark (2010) with no consideration or mention of 3D imaging/navigation. 3D navigation was not considered necessary at the time of regulatory clearance nor is it considered necessary at this time. The vast majority of the 29,000 cases performed to date have been performed under 2D fluoroscopic imaging. The system was designed to be used with 2D imaging. Placement of surgical implants (screws) across the sacroiliac joint with a lateral to medial trajectory has been a standard orthopedic procedure for many years. The surgical approach and implant trajectories are well established clinically and are well documented in the clinical literature. Orthopedic trauma surgeons will frequently place implants across the SI joint, across the sacrum, and ultimately across the contralateral SI joint (a trans-iliac trans-sacral trajectory). iFuse implants are not typically placed beyond the foramen and thus are easier and safer to place compared to screws placed for pelvic trauma. The published clinical literature (Miller 2012, Cher 2015) that described the low rates of implant malposition, were based upon procedures performed with 2D fluoroscopic imaging. Indeed, all of the clinical literature that supports the safety, effectiveness, and durability of the iFuse Implant System was based upon procedures performed with 2D fluoroscopic imaging. It is understood that 3D navigation systems such as the Medtronic O-arm are becoming more prevalent in the UK, in Europe and in the US. However, use of 3D navigation is not currently the community standard for the majority of spine procedures including MIS SI joint fusion. It may well be that at some point in the future, 3D navigation becomes the standard for MIS SI joint fusion. However, at this point in	To be discussed with clinical experts.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
		time, 3D navigation is not necessary and is not routinely recommended for the iFuse procedure. Because of the increased interest in 3D navigation, SI-BONE have created instruments that facilitate the use of 3D navigation systems, including the Medtronic O-arm, for the iFuse procedure. However, the vast majority of surgeons do not currently use 3D navigation for the iFuse procedure.	
Clinical submission – Section 4.1	The documents that you provided are an EN ISO 13485 certificate and instructions for use. In order to ensure that iFuse is CE marked we require additional certification. Would your regulatory affairs manager be able to return copies of the required certificates as soon as possible please? The certificates we require depend on the classification of the device according to the Medical Device Directive (93/42/EEC) e.g. Class I, Class IIa, Class IIb or Class III. Your regulatory affairs manager will know which certificates are required for your device.	The company sent through the relevant documents attached to the email below: James. Please see the documents provided by our VP of regulatory. Attached are the: * Declaration of Conformity (DOCs) for iFuse and instruments * CE certificate for our sterilization facility, Steris, Inc. * IFUs for iFuse Implant System (iFuse and iFuse-3D)	iFUSE is CE marked.
Clinical submission - Section 4.3	Why was regulatory approval for iFuse withdrawn from Canada in November 2017?	<u>EAC's interpretation of answer following a teleconference with the manufacturer:</u> Regulatory approval was withdrawn due to marketing issues. There was a problem obtaining a distributor for iFuse in Canada so the product was withdrawn by the company whilst they sought regulatory approval in other countries in line with the company's strategic aims. The product was not withdrawn due to device safety concerns. <u>Added by the manufacturer:</u> The iFuse Implant System previously received regulatory clearance in Canada. A small number of cases were performed in 2015-2016. SI-BONE has elected not to renew the regulatory registration for business reasons. No safety notifications were issued and Canadian regulatory concerns were not a factor in the company decision to not renew	None.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
		regulatory registration to market iFuse in Canada. This was strictly a business/marketing decision.	
Clinical submission - Section 7.1	SI Bone state that published studies are "continuously monitored". How is this achieved?	<u>EAC's interpretation of answer following a teleconference with the manufacturer:</u> SI Bone endeavour to monitor all published studies and not just those which are sponsored by the company. Employees at SI Bone carry out weekly searching for newly published studies related to iFuse. This searching forms part of the company's compliance monitoring. The manufacturer did not have anything to add.	None.
Clinical submission - Section 7.2.2	The link provided for the PDFs does not work.	Doug agreed to get a working URL to us and to provide references for the 53 publications.	New URL for the PDFs will be sent by the company.
Clinical submission - Section 7.3.1	The EAC noted that the two open SI joint fusion groups in Ledonio (2014a) and Ledonio (2014b) had the same numbers of patients and the baseline characteristics were identical. The EAC asked the company whether the same patients had been used in both studies?	<u>EAC's interpretation of answer following a teleconference with the manufacturer:</u> According to the company, the open SI joint fusion groups used in both studies were the same cohort. However, the patients receiving minimally invasive SI joint fusion with iFuse were different in each paper. The company suggested using the review by Heiney et al. (2015) to help to determine cohort overlap in studies.	None.
General question on Economic submission	The EAC asked the company what programme will be used for the economic model (e.g. Excel, treeage, etc.) in order to ensure that the relevant EAC staff are available to work on the model during the Christmas period.	Deirdre Blissett, the health economist responsible for building the economic model, stated that Excel would be used.	None.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
General email following up EAC queries	Thank you for sending these CE marking certificates through to me. The information you've sent through is sufficient. Have you been able to respond to my previous queries yet? If you already have sent this through to me then I apologise. Would you be able to send this to me once again, but also copy in my Cardiff University email address (ccd into this email)? Since the ransomware attack on the NHS many emails from non-NHS addresses do not make it to us. It might be a good idea to copy my Cardiff University email address into all future correspondence.	The manufacturer sent through an email they previously sent. This email had been blocked.	None.
Clinical submission - section B	I have a query regarding the study list you kindly provided. In the notes section there are a number of studies where it has been noted the site has been counted in another study e.g. Rudolf et al. (2012) "site counted in SIFI (Duhon 2015)". Does this mean that the site was counted in the study but not the patients? So for the study by Rudolf et al. (2012) the 50 study patients were not included in the SIFI trial and the paper by Duhon et al. (2015) but the site contributed to the trial when it began enrolling? I'd just like to make sure that I have the correct understanding because that is quite an important distinction.	<u>Response from the manufacturer</u> We are currently revising the Excel table with the studies and the sites information. As you describe in your email, in most instances, a site may have participated in multiple studies, however, in almost all cases the patients are unique. We will work to clarify. The manufacturer sent through an updated Excel table.	Affects which studies are included by the EAC.
Clinical submission - section B	Just a quick email to ask about the study by Sachs et al. (2016). In the Excel spreadsheet you provided you said that all the participants had previously been counted. Would you be able to let me know in which studies they had been used please? I can see that patients	<u>Response from the manufacturer</u> Reconciliation of patients in retrospective studies can be challenging, so thank you for attention to detail, and your patience. Upon further investigation, below are the details for the patients involved in the Sachs publications: Sachs 2014 (no change) and Sachs 2016 (updated).	Affects which studies are included by the EAC.

<table>
<tr><th>Submission Document Section/Sub-section number</th><th>Question / Request</th><th>Response</th><th>Action / Impact / Other comments</th></tr>
<tr><td></td><td>from D Sachs have been presented on Sachs et al. (2014) but what about the others?</td><td>Please see updated spreadsheet dated December 6, 2017.

Sachs 2014: 144 patients from 6 sites, mean 16-month Follow-up
No change in site or patient count.

<table>
<tr><td>Site (Physician)</td><td>Patients</td><td>Previously Counted</td><td>Unique Patients</td></tr>
<tr><td>Holt</td><td>33</td><td>-</td><td>33</td></tr>
<tr><td>Cummings</td><td>25</td><td>19 (INSITE)</td><td>6</td></tr>
<tr><td>Gundanna</td><td>23</td><td>-</td><td>23</td></tr>
<tr><td>Shamie</td><td>6</td><td>-</td><td>6</td></tr>
<tr><td>Graven</td><td>18</td><td>-</td><td>18</td></tr>
<tr><td>Sachs</td><td>39</td><td>39 (39 of 40 from Sachs 2013)</td><td>-</td></tr>
<tr><td></td><td></td><td></td><td>86</td></tr>
</table>
Sachs 2016: 107 patients from 7 sites, mean 3.7-years Follow-up

All 7 sites are previously counted as being part of SIFI and/or INSITE. I originally thought since the sites were involved in SIFI or INSITE, so were the patients. However, given the long-term follow-up (mean 3.7 years), the patients involved in this retrospective study were treated before SIFI and INSITE, and thus not counted in previous publications. All but Dr Sachs' patients, who were previously counted in Sachs 2013 and Sachs 2014 articles. This is confirmed by the publications' statement under Methods, "The study includes patients at one center (D Sachs), which has been previously reported."

<table>
<tr><td>Site (Physician)</td><td>Patients</td><td>Previously Counted</td><td>Unique Patients</td></tr>
<tr><td>Kovalsky</td><td>23</td><td>-</td><td>23</td></tr>
<tr><td>Meyer</td><td>6</td><td>-</td><td>6</td></tr>
<tr><td>Kondrashov</td><td>7</td><td>-</td><td>7</td></tr>
<tr><td>Redmond</td><td>11</td><td>-</td><td>11</td></tr>
<tr><td>Limoni</td><td>8</td><td>-</td><td>8</td></tr>
</table>
</td><td></td></tr>
</table>

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
		<table><tr><td>Harvey</td><td>6</td><td>-</td><td>6</td></tr><tr><td>Sachs</td><td>46</td><td>40 (Sachs 2013)</td><td>6</td></tr><tr><td colspan="3"></td><td>67</td></tr></table>	
Economic submission – section C	Would it be possible to send us a UK price list for iFuse please?	A price list for iFuse was provided by the manufacturer. Response from the manufacturer Please find the iFuse Pricelist attached	Will be used in the EAC's critique of the economic model submitted by the manufacturer.
Economic submission – section C	Apologies if this seems like a silly question. To clarify, the prices shown are for a single implant? I notice from the literature that 3 implants are often used. So am I correct in thinking that 3 x 7.5mm implants at £1500 each would come to £4500? I'm just making sure that when you buy an implant and it says "1" under quantity it isn't referring to a pack of 3 implants rather than an individual implant.	Response from the manufacturer Yes the prices are per implant but I would use the £1155 per implant price as this is by far the most commonly used implant.	Will be used in the EAC's critique of the economic model submitted by the manufacturer.
Company economic model	The EAC asked Mr Mark Thomas the following questions: Non-surgical pathway • What would be the most appropriate HRG code for steroid injections? • Are RFA procedures carried out as a day case or outpatient case? • What would be a typical prescription for pain management for a patient who still has chronic pain following conservative treatment or surgery? • What proportion of patients continue to have steroid injections after their initial injection? o For patients that have more than 1 injection, what	Response from Mr Mark Thomas Non-surgical pathway • What would be the most appropriate HRG code for steroid injections? Not sure – will find out • Are RFA procedures carried out as a day case or outpatient case? Day case • What would be a typical prescription for pain management for a patient who still has chronic pain following conservative treatment or surgery? Very variable. I assume you mean what medication would they be on? I would expect them to be on an opiate such as codeine or possibly Tramadol. Often they will require transdermal patches for sustained pain relief	The responses will be used by the EAC to modify the company's economic model.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
	percentage would still be receiving steroid injections at 2 years? • How often are the steroid injections given? • What happens to patients if they no longer receive steroid injections? • What proportion of patients would receive radiofrequency ablation? <u>Surgical</u> • If a patient has successful surgery would you expect them to still require any pain management prescription? • What percentage of patients having open surgery would have anterior / posterior / lateral? • Please comment on the consumables, number used and unit cost for the different surgery types, if you are able to (please see **Table 1**):	• What proportion of patients continue to have steroid injections after their initial injection? Approx 50% will settle with one injection and some will go on to have multiple. I don't have the absolute numbers but my approach is that if the injections are successful but only temporary, there comes a point to stop and consider surgery as a more permanent solution. o For patients that have more than 1 injection, what percentage would still be receiving steroid injections at 2 years? Only a small number • How often are the steroid injections given? Depends upon how long they last. The injections shouldn't be seen as a regular, routine top up every 6 months or so. • What happens to patients if they no longer receive steroid injections? One would assume that either the pain was at a reasonable level, they were referred through to the pain team for denervation or referred for surgery. • What proportion of patients would receive radiofrequency ablation? Nationally – no idea. In my hands, very small as evidence doesn't support it. <u>Surgical</u> • If a patient has successful surgery would you expect them to still require any pain management prescription? No – not prescription medication • What percentage of patients having open surgery would have anterior / posterior / lateral? Currently I would expect the vast majority to have MIS lateral access surgery such as iFuse. I am not aware of anyone doing anterior surgery for the sacroiliac joint. I'm not sure what you mean by posterior surgery, esp. as in the table you list pedicle screws. These are not used in sacroiliac joint fusion. Your consumables for the iFuse look about right.	

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
Company economic model	The EAC asked Mr Boszczyk the following questions: <u>Non-surgical pathway</u> • What would be the most appropriate HRG code for steroid injections? • Are RFA procedures carried out as a day case or outpatient case? • What would be a typical prescription for pain management for a patient who still has chronic pain following conservative treatment or surgery? • What proportion of patients continue to have steroid injections after their initial injection? o For patients that have more than 1 injection, what percentage would still be receiving steroid injections at 2 years? • How often are the steroid injections given? • What happens to patients if they no longer receive steroid injections? • What proportion of patients would receive radiofrequency ablation? <u>Surgical</u> • If a patient has successful surgery would you expect them to still require any pain management prescription? • What percentage of patients having open surgery would have anterior / posterior / lateral?	Mr Boszczyk asked to arrange a phone call for 19/01/18 to discuss the queries. The phone call was rearranged for 22/01/18. The EAC's interpretation of Mr Boszczyk's answers to each question has been presented in red: <u>Non-surgical pathway</u> • What would be the most appropriate HRG code for steroid injections? Uncertain as steroid injections would be administered by pain consultants. However, it is likely that a HRG code would be similar for all steroid injections regardless of the target joint. • Are RFA procedures carried out as a day case or outpatient case? Uncertain. Pain consultants are likely to know. However, Mr Boszczyk suspects it would be a day case procedure. • What would be a typical prescription for pain management for a patient who still has chronic pain following conservative treatment or surgery? Uncertain on a specific prescription. However, non-steroidal medication would be used. • What proportion of patients continue to have steroid injections after their initial injection? Uncertain as pain consultants administer these injections. o For patients that have more than 1 injection, what percentage would still be receiving steroid injections at 2 years? Uncertain as pain consultants administer these injections.	The responses will be used by the EAC to modify the company's economic model.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
	• Please comment on the consumables, number used and unit cost for the different surgery types, if you are able to (please see **Table 1**):	• How often are the steroid injections given? Uncertain as pain consultants administer these injections. • What happens to patients if they no longer receive steroid injections? Uncertain as pain consultants administer these injections. • What proportion of patients would receive radiofrequency ablation? Uncertain as pain consultants administer these injections. <u>Surgical</u> • If a patient has successful surgery would you expect them to still require any pain management prescription? Temporary pain relief would be required during recovery for the first few weeks. This would be non-steroidal pain management. • What percentage of patients having open surgery would have anterior / posterior / lateral? Uncertain regarding proportions of patients receiving anterior/posterior/lateral surgery. Open surgery (fixation with screws) is not done often now as it is an arduous procedure. However, posterior SIJ fixation with screws would be carried out more frequently than anterior/lateral. • Please comment on the consumables, number used and unit cost for the different surgery types, if you are able to: Posterior SIJ fixation would be the most expensive procedure. The procedure takes a long time to carry out and is sometimes carried out as two separate procedures. Therefore, the higher consumable costs presented for posterior SIJ fixation is highly likely.	

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
Company economic model	The EAC asked Mr Boszczyk a few additional questions during a phone call on 22/01/18: • How many follow-up visits would you expect for iFuse in the first year? • Will an iFuse implant ever need replacing? • Do iFuse patients receive post-op physiotherapy appointments?	The EAC's interpretation of Mr Boszczyk's answers to each question has been presented in red: • How many follow-up visits would you expect for iFuse in the first year? Mr Boszczyk's patients usually receive 2 follow-up visits in the first year (one at 6 weeks and all being well with the patient another at 12 months). However, patients of some clinicians will receive 3 follow-up visits. • Will an iFuse implant ever need replacing? No. Provided the bone fuses to the implant there will be no need to replace the device. Revision surgery is sometimes required but this will be early on following surgery and not late. • Do iFuse patients receive post-op physiotherapy appointments? Yes. This aids recovery and some patients will receive up to 6 sessions. However, this is not standardised and each physiotherapist will do have their own preferences for the number of sessions a patient will receive.	The responses will be used by the EAC to modify the company's economic model.
Company economic model	The EAC asked Mr Noordeen the following questions: <u>Non-surgical pathway</u> • What would be the most appropriate HRG code for steroid injections? • Are RFA procedures carried out as a day case or outpatient case? • What would be a typical prescription for pain management for a patient	Mr Noordeen apologised for not replying and said he would get respond to the queries on Friday (19/01/18). The EAC received no response from Mr Noordeen.	None.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
	who still has chronic pain following conservative treatment or surgery? • What proportion of patients continue to have steroid injections after their initial injection? o For patients that have more than 1 injection, what percentage would still be receiving steroid injections at 2 years? • How often are the steroid injections given? • What happens to patients if they no longer receive steroid injections? • What proportion of patients would receive radiofrequency ablation? <u>Surgical</u> • If a patient has successful surgery would you expect them to still require any pain management prescription? • What percentage of patients having open surgery would have anterior / posterior / lateral? • Please comment on the consumables, number used and unit cost for the different surgery types, if you are able to (please see **Table 1**):		
Company economic model	The EAC clarified a few of the questions for Mr Mark Thomas and made a few additional queries in response to Mr Thomas' previous response: <u>Non-surgical pathway</u>	<u>Response from Mr Mark Thomas:</u> <u>Non-surgical pathway</u> • What would be a typical prescription for pain management for a patient who still has chronic pain following conservative treatment or surgery?	The responses will be used by the EAC to modify the company's economic model.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
	• What would be a typical prescription for pain management for a patient who still has chronic pain following conservative treatment or surgery? I should have made this question clearer. We wanted to know what medication regimen patients with SIJ pain follow. We are aware that a patient would be taking an opiate. However, the company in their economic model have priced a daily regimen/prescription for a patient with SIJ pain e.g. 2 x specific tablet (at specified dose), 2 x another table (at specified dose). We wanted to canvass your opinion on what a typical pain relief regimen/prescription for a patient with SIJ pain would be to give us an informed input for the model. With regards to the trans-dermal patch you mentioned, would this be Buprenorphine? Would you expect nearly every patient to be using this? <u>Surgical</u> • What percentage of patients having open surgery would have anterior / posterior / lateral? Again, I should have made the question clearer. We wanted to ask about patients receiving SIJ fixation using screws here. In the literature it's described as open surgery but I should have been clearer. The company compare surgery with iFuse to SIJ fixation with screws in	I should have made this question clearer. We wanted to know what medication regimen patients with SIJ pain follow. We are aware that a patient would be taking an opiate. However, the company in their economic model have priced a daily regimen/prescription for a patient with SIJ pain e.g. 2 x specific tablet (at specified dose), 2 x another table (at specified dose). We wanted to canvass your opinion on what a typical pain relief regimen/prescription for a patient with SIJ pain would be to give us an informed input for the model. With regards to the trans-dermal patch you mentioned, would this be Buprenorphine? Would you expect nearly every patient to be using this? I don't think that there is a 'standard' pain regime Long term NSAIDS are generally seen as bad news so I wouldn't include them Tablet wise therefore, I would expect all to need a low dose opiate with paracetamol either as a combined tablet such as Zapain / Cocodamol or as separates, Paracetamol 1G and codeine 60 mg 4x daily. If Tramadol is needed then quite quickly this would be changed to a patch such as buprenorphine as long term cover. <u>Surgical</u> • What percentage of patients having open surgery would have anterior / posterior / lateral? Again, I should have made the question clearer. We wanted to ask about patients receiving SIJ fixation using screws here. In the literature it's described as open surgery but I should have been clearer. The company compare surgery with iFuse to SIJ fixation with screws in one of their economic models. From my understanding SIJ fixation with screws can be done through an anterior, posterior or lateral approach. The model makes an assumption on the proportion of patients receiving	

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
	one of their economic models. From my understanding SIJ fixation with screws can be done through an anterior, posterior or lateral approach. The model makes an assumption on the proportion of patients receiving anterior/posterior SIJ fixation with screws. We wanted to canvass your opinion on this to give us an informed input for the model.	anterior/posterior SIJ fixation with screws. We wanted to canvass your opinion on this to give us an informed input for the model. There are 2 ways of stabilising the SIJ with screws but both are from the lateral approach. The traditional 'open' approach through a large buttock dissection and grafting of the joint. Those screws would be cannulated screws as used in many other orthopaedics operations. This approach was time consuming, high morbidity and long length of stay. Screws can also be used percutaneously with a similar approach to iFuse. Without seeing their descriptions of alternative techniques, I can't comment further.	
Company economic model	The EAC sent Mr Noordeen the following request. Questions are listed in the next column, with answers in red. Following the lead team meeting on the 9th April for iFUSE, we are looking to add additional information about the procedures patients may have prior to iFUSE surgery.	1. Do patients require diagnostic or work up tests prior to surgery with iFUSE? If so, please could you list them. MRI Scan principally but also 3D CT 2. If you know them, please also list the associated costs or NHS reference codes Dont know 3. Are these required by all patients who will have iFUSE? YES 4. Will patients who continue with non-surgical treatments (and do not have surgery) also require these procedures? All need MRI only Surgical need 3D CT.	None.
Company economic model	The EAC sent Mr Thomas the following request. Questions are listed in the next column, with answers in red.	1. Do patients require diagnostic or work up tests prior to surgery with iFUSE? If so, please could you list them. History, examination, diagnostic injections as described in diagnosis of sacroiliac joint pain. So same work up whatever the treatment pathway	None.

Submission Document Section/Sub-section number	Question / Request	Response	Action / Impact / Other comments
	Following the lead team meeting on the 9th April for iFUSE, we are looking to add additional information about the procedures patients may have prior to iFUSE surgery.	2. If you know them, please also list the associated costs or NHS reference codes No! 3. Are these required by all patients who will have iFUSE? Yes 4. Will patients who continue with non-surgical treatments (and do not have surgery) also require these procedures? Yes	

Table 1| Cost questions asked by the EAC to clinical experts.

Consumable Costs Open - Anterior	Number	Unit cost	Clinical expert comment
Plates and 4 Screws	2	£250.00	
Cannulated screw with washer	1	£100.00	
Drain	1	£60.00	
DBM	1	£500.00	
Stitches	3	£20.00	
Any other consumables?			
Consumable Costs Open - Posterior			
Two pedicle screws	2	£400.00	
One cross connecting rod	1	£250.00	
One PLIF cages	1	£900.00	
One BMB sponge	1	£1,200.00	
Two crew caps, nuts etc	2	75.00	
Any other consumables?			
Consumable Costs iFuse			
Surgical Implants	3	£1,155.00	
Surgical Accessories	1	£275.00	
Steinmann pins	3	£47.00	
Exchange pin	**1**	**£47.00**	
Drill **Any other consumables?**	**1**	**£131.00**	

iFUSE, supplementary report on extended time horizon

Following a request from MTAC, Cedar agreed to investigate the impact of an extended timeline on health economic model submitted by SI-Bone for iFUSE.

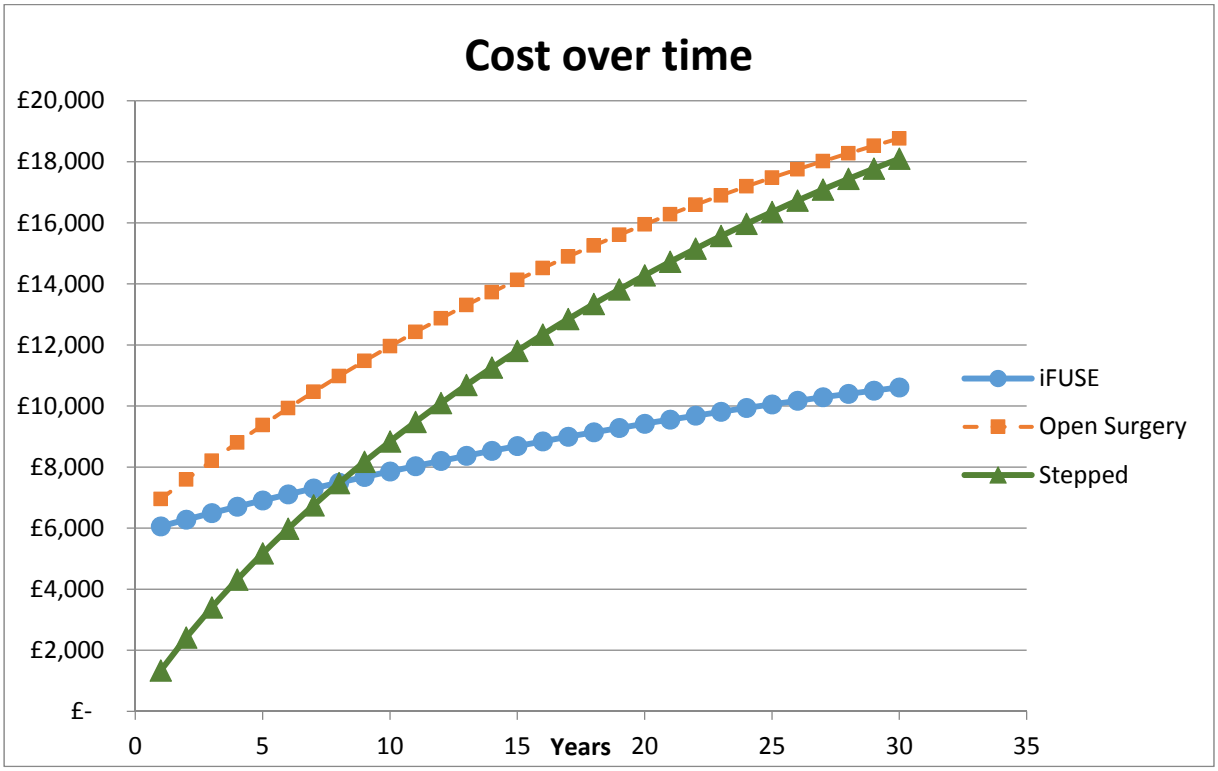
The following steps were taken:

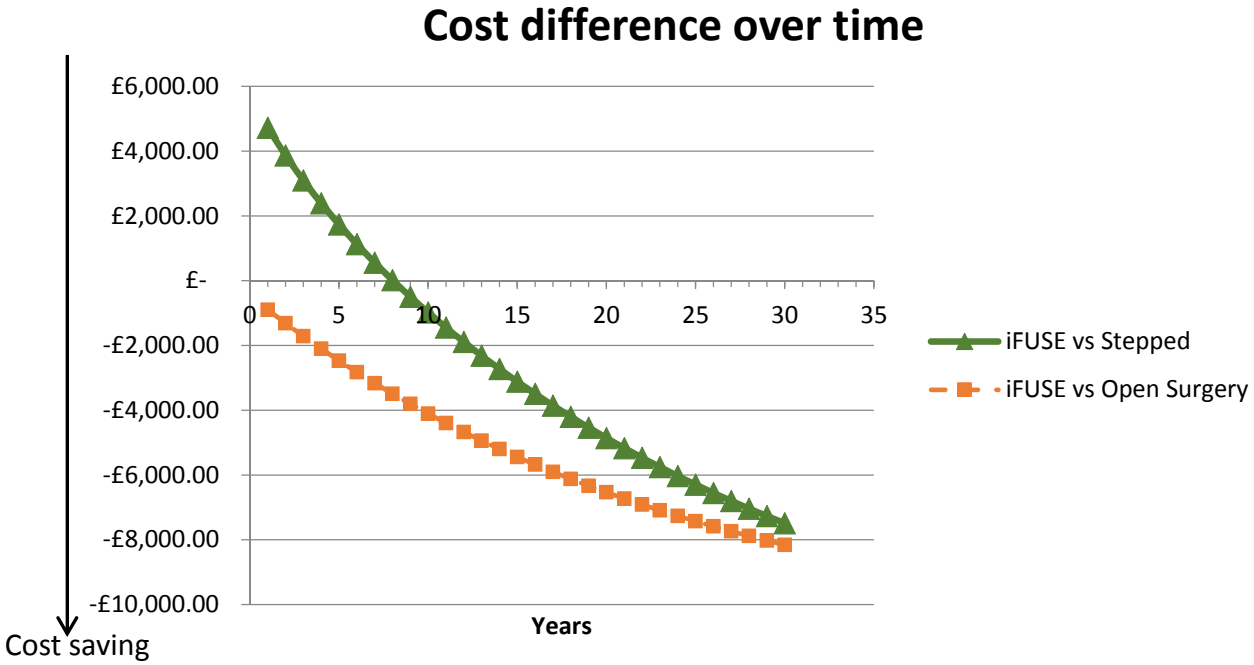
- Using the same transition probabilities, the tables showing number of patients in each treatment state was extended to 30 years
- Calculations in the results page were adjusted to take account of the extended 30 year period.
- Results tables and graphs were extended to show 30 year results
- Calculations in the results page were adjusted to take account of the extended 30 year period.
- Additional graphs were added to show the cost and cost saving over the 30 year period

These allow an insight into how the model behaves over a longer period of time, however it does not include all the steps that would be considered if the model had been originally created with this intention.

Limitations include:

- There is no mortality, it is assumed that all patients will survive another 30 years. In reality mortality will have a significant effect over a 30 year horizon. This is likely to reduce the cost saving due to iFUSE over time. Most of the iFUSE cost is at the start of the model, and most patients are pain free (zero cost) at 30 years. Thus removing patients from the model has only a small impact on cost. For the stepped pathway patients accumulate cost throughout the model (mainly from pain medication), so including mortality will lower the overall cost.
- The likelihood of moving from one state to another is constant for both iFUSE and conservative groups, as discussed in subsequent bullet points.
- There is no change in the likelihood of requiring a revision, assumes that a good iFUSE outcome remains pain free unless requiring revision. At present there is no long term data, and we do not know if this is the case. If pain increased, or additional revisions were required, the cost of iFUSE over a patient lifetime would be increased.
- For the conservative treatment arm, approximately 94% of patients are assumed to be treated with pain medication only by year 10, and remain in this state for the rest of the model. This may reflect the current situation. If in the future another treatment were available outcomes could improve, but the impact on costs would be unknown


Cost over time
£20,000
£18,000
£16,000
£14,000
£12,000
£10,000
£8,000
£6,000
£4,000
£2,000
£-
0
5
10
15
Years
20
25
30
35
iFUSE
Open Surgery
Stepped


Cost difference over time
£6,000.00
£4,000.00
£2,000.00
£-
-£2,000.00
-£4,000.00
-£6,000.00
-£8,000.00
-£10,000.00
0
5
10
15
20
25
30
35
Years
Cost saving
iFUSE vs Stepped
iFUSE vs Open Surgery

Cost per patient (negative value indicates cost saving)

	iFuse	Stepped	iFuse v Stepped
Year 1	£6,059	£1,337	£4,721.76
Year 9	£7,676	£8,171	-£494.57
Year 10	£7,856	£8,838	-£981.83
Year 15	£8,689	£11,806	-£3,117.17
Year 20	£9,419	£14,279	-£4,859.96
Year 25	£10,056	£16,354	-£6,298.46
Year 30	£10,611	£18,100	-£7,489.92