External Assessment Centre report

Title: iFuse implant system for treating chronic sacroiliac joint pain

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Declared interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
ASLR	Active straight leg raise test
CASP	Centre for Reviews and Dissemination and the Critical Appraisal Skills Programme
CBT	Cognitive behavioural therapy
CI	Confidence interval
CM	Conservative management
CT	Computerised tomography
EAC	External Assessment Centre
EQ-5D	EuroQol 5 dimension
FDA	Food and Drug Administration
HRQoL	Health-related quality of life
iMIA	iFuse Implant System Minimally Invasive Arthrodesis
INSITE	Investigation of Sacroiliac Fusion Treatment
LBP	Lower back pain
LOIS	Long-term follow-up in INSITE/SIFI
MAUDE	Manufacturer and User Facility Device Experience
MCID	Minimal clinically important difference
MCS	Mental component summary
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
NSM	Non-surgical management
ODI	Oswestry disability index
PCS	Physical component summary
PPGP	Post-partum pelvic girdle pain
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PT	Physical therapy
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
RFA	Radio-frequency ablation
SALLY	Sacroiliac Joint After Minimally Invasive Surgery With Titanium Implants
SD	Standard deviation
SF-36	36 item short form survey

SI	Sacroiliac
SID	Sacroiliac denervation
SIFI	Sacroiliac Joint Fusion With iFuse Implant System
SIJ	Sacroiliac joint
SIJF	Sacroiliac joint fusion
SRS22	Scoliosis Research Society Outcomes Questionnaire
TTO	Time trade-off
VAS	Visual Analogue Scale
vs.	Versus

1 Executive Summary

The company submission contained a total of 6 key studies and a further 28 studies listed as relevant. The EAC included 12 studies following its own literature search and assessment of studies listed as relevant by the company. Of these, two were RCTs, three were retrospective comparative studies and seven were non-comparative studies. The EAC also presented the results of a case report whilst discussing adverse events.

The EAC considered that on the whole the quality of the evidence was strong, particularly for comparative evidence on the use of iFuse vs. conservative/non-surgical management. However, a large number of studies were not included by the EAC due to patients being presented in other studies and this limited the evidence on the use of iFuse compared to open surgery considerably. The included evidence contained outcomes relevant to the scope.

The company's economic submission contained evidence not relevant to this assessment with no studies matching the scope. The company's economic submission showed iFuse to be cost saving compared to open surgery or a stepped pathway (conservative/non-surgical management).

Following changes to the model by the EAC, the cost savings when using iFuse in place of open surgery were lower. Using iFuse instead of a stepped pathway became cost incurring at a 7 year time horizon. Further analysis by the EAC showed that iFuse became cost saving when the time horizon was extended to 9 years.

On the whole, clinical evidence showed that iFuse improved pain, ODI and health-related quality of life and these improvements were higher in patients receiving treatment with iFuse than those receiving conservative/non-surgical management. The evidence showed that fewer revisions are required with iFuse compared with open surgery using screws. iFuse was shown to be cost saving compared to open surgery but cost incurring compared to a stepped pathway using the manufacturer's time horizon. However, iFuse became cost saving compared to a stepped pathway with a longer time horizon.

2.1 Overview and critique of company's description of clinical context

The company presents a thorough description of the clinical context. Numerous papers have been referenced to demonstrate that the sacroiliac (SI) joint can be damaged through acute or repetitive trauma and that the SI joint can be a source of pain. Further studies presented by the company highlight that the SI joint is a pain source in people with lower back pain.

The company reference a NICE guideline on low back pain and sciatica in over 16s (NG59) and NICE interventional procedures guidance on minimally invasive sacroiliac joint fusion surgery for chronic sacroiliac pain (IPG578). SI joint fusion is likely to be used as part of a stepped approach to chronic SI joint dysfunction whereby less invasive treatments, such as treatment with non-steroidal anti-inflammatory drugs and/or opioids and physiotherapy, are initially used. SI joint steroidal injections are the next treatment in the pathway when less invasive treatments fail. If patients do not receive benefit from SI joint steroidal injections then sacroiliac denervation by radio-frequency ablation (RFA) is used. Finally, if RFA of the sacroiliac joint does not provide benefit the patient can undergo open surgery to carry out SI joint fixation.

The iFuse device is intended to be used in order to carry out minimally invasive fusion of the SI joint. The technology is made up of triangular, titanium implants, three of which are typically used, and these are inserted across the SI joint to fuse the joint. The company envisages that the technology will replace most open surgical procedures and is also expected to replace some long term use of non-surgical treatments with minimal changes to how current services are organized or delivered.

The company's description of the clinical context is appropriate and relevant to the decision problem under consideration.

2.2 Critique of company's definition of the decision problem

It is not clear from the company's submission which studies are included. This lack of clarity with regards to included studies is discussed by the External Assessment Centre (EAC) later in the report (see section 2.2). For the purposes of the following critique the EAC will discuss the studies listed as "relevant" by the company.

Table 1| EAC's critique of the company's definition of the decision problem.

Decision problem	Company submission	Matches decision problem? (Y/N/partially)	EAC comment
Population	People with unresolved sacroiliac joint dysfunction.	Y	The majority of the studies listed as relevant by the company presented the use of iFuse in patients with sacroiliac joint (SIJ) dysfunction. One study (Cher et al. 2015) included patients requiring revision surgery following sacroiliac joint fusion (SIJF) with no indication of why the surgery was initially required.
Intervention	Sacroiliac joint fusion using the iFuse Implant System.	Y	The company modified the intervention to include the terms "sacroiliac joint fusion". This was deemed sensible by the EAC. All but one study listed as relevant by the company used iFuse for SIJF. One study (MacBarb et al. 2017) presented an *in vitro* study of iFuse 3-D and was outside of scope.
Comparator(s)	• Open sacroiliac joint fusion surgery using screw or cage systems. • Non-surgical or conservative management, including: o optimisation of medical therapy,	Partially	The company have added radiofrequency ablation as a comparator. The EAC feels this comparator was already covered by "sacroiliac joint denervation". Studies listed as relevant by the manufacturer included all listed comparators. However, non-

	○ individualised psychological and physical therapy with provision of adequate information and reassurance ○ steroid injections • Sacroiliac joint denervation • Radiofrequency ablation (RFA) of the lateral branches of sacral nerve roots.		surgical management includes a number of different treatments and the results are often not presented for each individual treatment.
Outcomes	**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	Partially	The company have added “medication (opioid use) use. The EAC feels this outcome was already covered by “back/sacroiliac joint pain relief (including medicine use and post-operative pain scores)”. Studies listed as relevant by the company present results for the majority of the outcomes listed in the scope. However, time to return to work/normal activities has not been presented in the relevant studies. Work status at baseline is often presented however, but not the time taken to return to work.

	• medication (opioid) use. **System outcomes** • procedure time and resources • length of hospital stay.		
Cost analysis	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.	Partially	The company's economic submission contained a paper on worker productivity of patients from the societal perspective and therefore does not match the scope (Savoss et al. 2006). The included study by Polly et al. (2016b) discusses SIJ block as a work up for SIJ pain determination and is therefore out of scope. Three other papers included by the company (Ackerman et al. 2013, Ackerman et al. 2014, Cher et al. 2016) were from a US payer perspective and were therefore outside of scope. The company submitted two models. One model focuses on a stepped pathway which included steroid injections, RFA and opioid pain management. The other model compares iFuse against SIJ fixation surgery using screw or cage systems. All comparators in the model are within scope. The company has chosen a 7 year time horizon to reflect differences in costs and consequences between iFuse and comparators. The company undertook sensitivity analysis.
Subgroups	• women of reproductive age • number of implants inserted • unilateral versus bilateral sacroiliac joint implants • previous lumbar surgery	Partially	One paper (Capobianco and Cher 2015) listed as relevant by the company presents a sub-group analysis of results presented in another study. This sub-group analysis compares outcomes for women with post-partum pelvic girdle pain (PPGP), women with no PPGP and men.

			No other papers listed as relevant by the company present results for the remaining sub-groups. However, the number of implants inserted, the number of patients receiving unilateral or bilateral implants and those who have undergone previous lumbar surgery are often presented in tables in the studies.

Special considerations, including issues related to equality

The EAC found that the company's submission addressed the specific equality issues identified in the scope. The company presented information on an equality issue with regards to women of reproductive age identified in the scope. The company state that "women of reproductive age having iFuse Implants on a single side (unilateral) may or may not be able to have a successful vaginal delivery". Furthermore, "if the woman has implants on both sides (bilateral) then a Caesarean section should be planned". However, the company state they "do not anticipate that there will be any equality issues relating to the assessment of the technology that may require special attention". The EAC did not identify any additional equality issues.

2 Clinical evidence

2.1 Critique of and revisions to the company's search strategy

The company states they, "continuously monitor the published literature for the presence of studies related to SI joint pain or SI joint fusion", and has kept a database of published literature relevant to the SI joint since 2012. However, no specific details were provided on how the company monitors these studies. In preparation for their submission the company carried out a search in Medline using a simplistic search. In light of the lack of detail on how the publication of new relevant studies is monitored, the simplistic search strategy and use of a single database, relevant studies may not have been identified. Therefore, the EAC conducted its own literature search using a comprehensive search strategy. The search made use of free text terms and medical subject headings and was used across databases identified in the Medical Technologies Evaluation Programme (MTEP) sponsor submission template and other databases. The company included information on unpublished manuscripts from trials with previously published manuscripts but did not appear to search trial registers. Both the company's and EAC's search strategies have been presented in Appendix A - Company and EAC literature search strategies and PRISMA diagrams

2.2 Critique of the company's study selection

The company's study selection was not clear. The company states they have identified a total of 55 studies. They provided a link to access 53 of these studies and referenced the other two. A total of 28 studies were listed as relevant however, later in their submission this was narrowed to 6 key publications. Three of the key publications listed by the company have been listed by the name of the trial and it is unclear which studies the company is referring to. Furthermore, one of the company's key publications is an unfinished study looking at 3 year outcomes in patients undergoing SIJF with iFuse (Long-term follow-up in INSITE/SIFI (LOIS) study see section 2.9 ongoing studies). Some results from this study have been shared with the EAC as academic in confidence. The inclusion and exclusion criteria used by the company were appropriate. The included studies present results on reoperation/revision rates in addition to other outcomes. However, there are studies which focus on revision rates exclusively and these were not included by the company. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams for both the EAC's and company's literature search are provided in Appendix A.

2.3 Included and excluded studies

The company identified 28 studies as relevant, and narrowed this further to 6 key publications. The EAC assessed the 28 relevant studies and requested extra information from the company regarding the participants for each study in order to ensure that there was no patient overlap between studies (Appendix B – Patient origin for company submitted studies, academic in confidence). The EAC identified 12 studies with patient overlap and these studies were not included by the EAC (Table 2).

The EAC excluded all 3 submitted reviews. Two did not separate results from open and minimal access surgery, and one used several methods for minimal access surgery. A further 2 papers were exluded as being out of scope.

One paper that was excluded by the company, has been included by the EAC as it reports outcomes for patients with previous spine fusion surgery.

In total the EAC included 12 studies that were relevant to this assessment, all of which were identified by the company. The EAC also identified one case report (Palmiere et al. 2017) which was discussed in section 2.7 (adverse events), but not included in the clinical evidence. A summary of the papers included by the EAC and company has been presented (Table 2). This table includes the EAC's reasons for disagreement regarding a study's inclusion/exclusion in this assessment.

Table 2| Studies included/excluded by the company and the EAC

Study	Included/ excluded by the company	Included/ excluded by the EAC	Reason for disagreement
INSITE trial			
Polly et al. (2016a)	✓	✓	
Polly et al. (2015)	✓	×	The 6 and 12 month results presented here are presented in Polly et al. (2016a).
Whang et al. (2015)	✓	×	The 6 month results presented here are presented in Polly et al. (2016a).
iMIA trial			
Dengler et al. (2017b)	✓	✓	
Dengler et al. (2016)	✓	×	This study is outside of scope as it reports leg pain. The 6 month results from the iMIA trial have been presented in Sturesson et al. (2017) and in Dengler et al. (2017b) alongside 1 year results.
Sturesson et al. (2017)	✓	×	The 6 month results presented here are presented in Dengler et al. (2017b).
SIFI trial			
Duhon et al. (2016)	✓	✓	
Duhon et al. (2016)	✓	×	The 6 and 12 month results presented here are presented in Duhon et al. (2016).

Duhon et al. (2013)	✓	×	The 6 month results presented here are presented in Duhon et al. (2016).
Capobianco and Cher (2015)	✓	✓	
Cher and Polly et al. (2016)	✓	×	The results from the SIFI trial are compared to a national representative cross-sectional survey.
Studies using multiple trials as data sources			
Dengler et al. (2017a)	✓	×	The results present a pooled analysis of previously published data from the INSITE, iMIA and SIFI trial. This paper presents a pooled analysis and predictors of outcomes following conservative and minimally invasive surgical management of SIJ pain. There are differences between what is permitted in terms of conservative/non-surgical management between the studies. Papers from the individual trials have been included by the EAC and they include more information regarding results and patients than the pooled analysis.
Polly et al. (2016b)	✓	×	The study looked at the effect of SIJ block to confirm the presence of SIJ dysfunction.
Comparative studies			
Smith et al. (2013)	✓	×	All iFuse patients were included in other studies (the company did not specify which studies).
Ledonio et al. (2014a)	✓	×	Some patients were included in the INSITE trial.
Ledonio et al. (2014b)	✓	×	All iFuse patients were reported in another study and some of these patients were included in the INSITE trial.
Spain and Holt (2017)	✓	✓	
Vanaclocha et al. (2018)	✓	✓	
Case series studies			

Bornemann et al. (2017)	✓	✓	
Cher et al. (2015)	✓	✓	
Miller et al. (2013)	✓	✓	
Rudolf and Capobianco (2014)	✓	✓	
Sachs et al. (2016)	✓	✓	
Vanaclocha et al. (2014)	✓	×	Patients from this study were presented in a later study (Vanaclocha et al. 2018).
Schroeder et al. (2014)	×	✓	This study was noted by the company in their submission but was not included. The EAC felt the study should be included as it reports outcomes for patients who have had previous spine fusion surgery.
Case report			
Palmiere et al. (2017)	-	✓ Included in adverse events section only	This was not included by the company in their submission. The EAC did not carry out a full data extraction or critical appraisal as this was only a case report. However, the EAC has referenced this paper in the adverse events section.
Reviews			
Lingutla et al. (2016)	✓	×	Results for open and minimal SIJF are not presented separately.
Heiney et al. (2015)	✓	×	Results for two methods of SIJF are not presented separately.
Zaidi et al. (2015)	✓	×	Results for open and minimal SIJF are presented separately. However, multiple methods of minimal SIJF have been included and are not presented separately.
***in vitro* study**			
MacBarb et al. 2017	✓	×	The paper focuses on iFuse 3-D, which is outside of scope. In addition, the study assesses the

			use of iFuse 3-D in sheep and this is also out of scope.
✓ = included; × = excluded; - not identified.			

In the following study summary table (Table 3) the intervention, comparator (if applicable), participants and outcomes have been coded as follows:

	Fully included within the scope
	Partially included within the scope
	Not consistent with the scope

In addition to the number of withdrawals in each study, the EAC has also included the number of “cross-over” patients from the two included RCTs (Dengler et al. 2017b and Polly et al. 2016a). Study protocols for both RCTs allowed patients in the non-surgical/conservative management treatment groups to cross-over to surgical treatment after 6 months if they felt no benefit from non-surgical treatment/conservative management.

Table 3| Summary of studies included by the EAC ordered by comparator and study design.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
iFuse vs. conservative management						
Dengler et al. (2017b)	Non-blinded RCT comparing minimally invasive SIJF to conservative management. Intervention: iFuse. ● Comparator: CM consisting of optimisation of medical therapy, individualised physiotherapy and information and patient reassurance as part of a multifactorial treatment. ●	109 patients enrolled with 6 patients withdrawing prior to randomisation. 103 patients randomised (SIJF n=52; CM n=51). SIJF: mean age (years) 49.4 (range 27-70), 38 females (73.1%). CM: mean age (years) 46.7 (range 23-69), 37 females (72.5%). SIJF prior treatment: physical therapy n=32 (61.5%), prolotherapy n=0 (0%), steroid SIJ joint (SIJ) injections n=37 (71.2%), RFA n=11 (21.2%), history of prior lumbar fusion n=18 (34.6%). CM prior treatment: physical therapy n=27 (52.9%), prolotherapy	**Relevant to scope:** Low back pain (LBP) improvement at 6 and 12 months; ODI at baseline, 3, 6 and 12 months; EQ-5D at baseline, 3, 6 and 12 months, SIJ function, patient depression, patient satisfaction, revisions and adverse events. ● **Not relevant to scope:** Leg pain. ●	Mean LBP improvement and ODI at 6 months and 12 months were significantly higher in the SIJF group than the CM group. Health-related quality of life (HRQoL) was significantly higher at 12 months in the SIJF group than the CM group. The same numbers of adverse events were observed in both treatment groups.	Withdrawals: 6 patients (4 assigned to CM, 2 to SIJF) withdrew prior to receiving any intervention. 5 patients withdrew between baseline-12 months (2 SIJF patients between 6-12 months, 2 CM patients between 1-3 months and 1 CM patient between 6-12 months). Cross-over: 21/49 CM patients at 6	Data for this paper were obtained from the iMIA trial. There is a previous publication (Sturesson et al. 2017) which presents outcomes for 6 months. The study was not blinded. The study was sponsored by SI-BONE manufacturer. The sponsor provided tools for electronic data capture, helped to perform data monitoring, source verification, cleaning and statistical analysis and prepared an initial draft of the study manuscript.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		n=0 (0%), steroid SIJ injections n=38 (74.5%), RFA n=6 (11.8%), history of prior lumbar fusion n=19 (37.3%). Multi-centre (Belgium n=2 centres, Germany n=3 centres, Italy n=3 centres, Sweden n=1 centre). Follow-up time: 12 months. Patients with LBP originating from the SIJ. ●			months crossed-over to surgical treatment. <u>Number of participants at each stage:</u> Baseline: CM=52, SIJF=51 3 months: CM=48, SIJF=52 6 months: CM=49, SIJF=52 12 months: CM=25, SIJF=49	One author is an employee of SI Bone. Another four authors are consultants to SI-BONE. CM patients were permitted to "cross-over" to SIJF after 6 months if they felt they had little benefit from CM. 21/49 (43%) CM patients crossed over to SIJF at 6 months. The authors used last-observation carried forward to estimate CM values at 12 months for use in their comparisons. This method is commonly used when there are missing data. Whilst not ideal, this was used to overcome the reduction in patients receiving CM following cross-over to SIJF. The last-

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
						observation carried forward only affects values for CM at 12 months and does not affect comparisons at 6 months.
Polly et al. (2016a)	Non-blinded RCT comparing minimally invasive SIFJ to non-surgical management. Intervention: iFuse. ● Comparator: non-surgical management (NSM) consisting of pain medications, physical therapy, intraarticular SIJ steroid injections and RFA of lateral branches of the sacral nerve roots. Therapy was delivered in a stepwise fashion to address pain and	159 patients enrolled with 1 patient withdrawing prior to randomization. 158 patients randomised (SIJF n=109; NSM n=49). 148 patients received their allocated treatment (SIJF n=102; NSM n=46). SIJF mean age 50.2 years (SD range 25.6-71.7), 75 females (73.5%). NSM mean age 53.8 years (SD range 29.5-71.1), 28 females (60.9%). SIJF prior treatment: physical therapy n=71 (69.6%), steroid SIJ injection n=85 (83.3%),	**Relevant to scope:** Pain score improvement, ODI and EQ-5D at 6, 12 and 24 months, patient satisfaction, opioid use, adverse events, revision surgeries. ● **Not relevant to scope:** Predictors of SIJF and NSM success. ●	Pain scores, disability index and quality of life of patients receiving SIJF were significantly lower at 6, 12 and 24 months following the procedure. A non-significant decrease in disability index and increase in quality of life was observed at 6 months in the NSM group. Pain scores at 6 months were significantly lower for SIJF patients than those for	1 patient withdrew prior to randomisation. 10 patients (3 assigned to NSM, 7 assigned to SIJF) withdrew prior to receiving any intervention. A further 15 patients withdrew between baseline-24 months (2 NSM patients between 1-3 months, 1 SIJF patient between 3-6	Data for this paper were obtained from the INSITE trial. There are two previous publications, Whang et al. (2015) which presents 6 month results and Polly et al. (2015) which presents 6 and 12 month outcomes. The study was not blinded. The study was sponsored by SI-BONE manufacturer. The study manuscript was written jointly by the authors and SI-BONE; statistical analyses were

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
	disability according to each individual's needs. ●	RFA n=21 (20.6%), prior lumbar fusion n=41 (40.2%). NSM prior treatment: physical therapy n=36 (78.3%), steroid SIJ injection n=42 (91.3%), RFA n=4 (8.7%), prior lumbar fusion n=17 (37%). Multi-centre (19 centres in the USA). Follow-up time: 24 months. Patients with chronic SIJ dysfunction. ●		NSM patients. Quality of life and patient satisfaction was significantly higher for SIJF patients than NSM patients at 6 months. SIJF was associated with a higher number of adverse events and some patients required revisions.	months, 1 SIJF patient between 6-12 months, 2 SIJF patients between 12-18 months and 9 SIJF patients between 18-24 months. <u>Cross-over:</u> 39/44 NSM patients at 6 months crossed-over to surgical treatment. <u>Number of participants at each stage:</u> Baseline: NSM=46, SIJF=102 6 months: NSM=44, SIJF=101	completed by SI-BONE. Two of the study authors are paid consultants to SI-BONE and another two are employees of SI-BONE. NSM patients were permitted to "cross-over" to SIJF after 6 months if they felt they had little benefit from NSM. 39/46 (84.8%) patients crossed-over to SIJF. It appears that a per-protocol approach was followed by the authors for 12 and 24 months data. Therefore, the numbers of patients in the NSM and SIJF groups at 12 and 24 months are very different. Therefore, the differences in

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
					12 months: NSM=5, SIJF=100 24 months: NSM=5, SIJF=89	outcomes between NSM and SIJF at 12 and 24 months should be treated with caution. The authors state that 9 patients were lost to follow up despite multiple attempts to contact them.
Vanaclocha et al. (2018)	Retrospective study comparing SIJF with CM and sacroiliac denervation in patients with SIJ pain. Intervention: iFuse● Comparator: CM●, sacroiliac denervation (SID)●	423 patients enrolled, 406 patients received prior CM. 193 patients received SIJ infiltration and 152 responded positively and were included in the study (SIJF n=27, 17.7%, CM n=74, 48.7%, SID n=51, 33.6%. SIJF mean (range) age (years) 48.0 (25-69), 19 females (70.4%). CM mean (range) age (years) 51.4 (29-70), 36 females (57.1%).	**Relevant to scope:** Pain, ODI and pain medication use at baseline, 1 month after treatment and every 6 months thereafter. ● **Not relevant to scope:** Work status. ●	Patients treated with continued CM had no longer-term improvement in pain or disability, increased use of opioids and poor long-term work status. SID patients had intermediate improvement in pain and disability scores. SIJF patients had large improvement in SIJ pain,	Patients refused medical treatment n=17/423 (4%) Numbers of patients at 1, 2, 3, 4, 5 and 6 year follow-up: CM: 63, 52, 43, 34, 23 and 16. SID: 47, 41, 33, 23, 6 and 2.	Many patients had to undergo CM due to lack of insurance coverage for SIJF and sacroiliac denervation. Not all patients were followed-up for the same amount of time (mean follow-up time 4 years). Patients receiving CM treatment had significantly longer SIJ pain duration than SID and SIJF patients.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		SID mean (range) age (years) 48 (24-70), 25 females (53.2%). SIJF prior treatment: physical therapy for max 3 months n=27 (100%), SIJ infiltration n=27 (100%), surgery n=3 (11.1%) of which lumbar fusion n=2 (7.4%), pain treatment n=8 (29.6%) of which lumbar epidural steroid injection n=1 (3.7%) CM prior treatment: physical therapy for max 3 months n=74 (100%), SIJ infiltration n=74 (100%), surgery n=29 (46.1%) of which lumbar fusion n=27 (42.9%), pain treatment n=33 (52.4%) of which lumbar epidural steroid injection n=11 (17.5%) SID prior treatment: physical therapy for max 3 months n=51 (100%),		disability and a decrease in opioid use and good final work status.	SIJF: 27, 24, 20, 15, 6 and 1.	The numbers of patients in SID and SIJF treatment groups are low by 5 and 6 years.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		SIJ infiltration n=51 (100%), surgery n=17 (36.1%) of which lumbar fusion n=16 (34%), pain treatment n=19 (40.5%) of which lumbar epidural steroid injection n=6 (12.8%) Single centre (Spain). Follow-up time: 6 years; mean follow-up time (months): CM=44, SID=39 and SIJF=41. Patients with unresolved SIJ pain. ●				
iFuse vs. SIJ fixation with screws						
Spain and Holt (2017)	Comparative, retrospective cohort study. Intervention: SIJF using iFuse. ● Comparator: SIJ fixation with screws. ●	312 patients undergoing SIJ treatment (SIJ fixation with screws n=38, SIJF with iFuse n=274). Records were located for 292 patients (SIJ fixation with screws n=29, SIJF with iFuse n=263).	**Relevant to scope:** Revision rates. **Not relevant to scope:** None	The revision rate for SIJF with iFuse was lower than that for SIJ with screws.	None.	The study was sponsored by SI-BONE. SI-BONE staff helped with statistical analysis. One of the authors is a consultant to SI-BONE. Follow-up time in the SIJF with iFuse group

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		SIJF: mean (range) age (years) 54.3 (24-85), 166 females (63.1%). SIJ fixation with screws: mean (range) age (years) 46.6 (27-61), 16 females (55.2%). Single-centre (USA). Mean (median) follow-up time: SIJF=2.8 (3.2) years, SIJ fusion = 4.6 (4.9) years. People with SIJ dysfunction. ●				was shorter than the SIJ fixation with screws group because patients undergoing SIJ fixation underwent surgery approximately 6 years before those undergoing SIJF. This could have an impact on the number of revisions and 4 year cumulative revision rates observed in each group.
Non-comparative						
Bornemann et al. (2017)	Non-comparative, prospective study. Intervention: iFuse (SIJF). ●	24 participants enrolled SIJF mean (±SD, range) age (years): 54.9 (±14.5, 18-76), 22 females (91.7%) SIJF prior treatment: conservative management (100%) Single centre (Germany).	**Relevant to scope:** Pain score, ODI, adverse events and radiographic outcomes at baseline, 1, 3, 6, 12 and 24 months and postoperative	Visual analogue score (VAS) improved significantly after surgery through to 3 months, and was maintained thereafter. ODI score improved significantly after surgery and continued to	None.	The authors state that a detailed anamnesis was performed for all patients. However, there was a lack of information regarding patient's prior treatment and the patient demographics presented were very simplistic.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		Follow-up time: 24 months. Patients with SIJ syndrome. ●	complications. ● **Not relevant to scope:** None.	improve until 24 months. No adverse events, intraoperative complications, implant malpositioning or loosening was observed.		
Cher et al. (2015)	Non-comparative, retrospective study. Intervention: iFuse (SIJF). ●	11,388 patients with a total of 11,280 sides treated. Mean age (years): 55.8, 6,709 females (58.9%). Multi-centre (based on the data from two company-maintained databases). Follow-up time: database complaints between April 2009 and July 2014. No mean follow-up presented. Patients requiring revision surgery following SIJF. ●	**Relevant to scope:** Reoperation (revision) rates. ● **Not relevant to scope:** None.	Four-year survivorship free from implant revision was 96.46%. Revision rate did not differ by sex and was lower for age >65. 24% of revisions occurred within the first 30 days after surgery, 63.5% occurred within year 1.	None.	All authors contributed toward data analysis, drafting and revising the paper and are SI-BONE employees.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
Duhon et al. (2016)	Non-comparative, prospective study. Intervention: iFuse. ●	194 patients enrolled. 172 patients received treatment. SIJF: mean age (range) 50.9 (23.5-71.6), 120 females (69.8%). SIJF prior treatment: physical therapy n=111 (64.5%), steroid SIJ injection n=162 (94.2%), RFA n=27 (15.7%), prior lumbar fusion n=76 (44.2%). Multi-centre (26 sites in the USA). Follow-up time: 24 months. People with SIJ dysfunction. ●	**Relevant to scope:** SIJ pain, ODI and quality of life at baseline, 12 and 24 months, opioid use, device-related adverse events, number of revisions, bone adherence and procedure resources. ● **Not relevant to scope:** None.	Pain and ODI were reduced at 3, 6, 12, 18 and 24 months post-procedure; this was significant between baseline and 24 months. HRQoL increased at 6, 12 and 24 months post-procedure; this was significant between baseline and 24 months.	10 patients withdrew prior to receiving treatment. 12 patients were removed from the study due to a site's non-compliance with the study protocol. A further 23 participants withdrew between baseline and 24 months (2 between 1-3 months, 2 between 3-6 months, 7 between 6-12 months, 8 between 12-18 months and 4 between 18-24 months)	Data for this paper were obtained from the SIFI trial. There are two previous publications: Duhon et al. (2013), which presents 6 month results, and Duhon et al. (2015) which presents 6 and 12 month outcomes. The study was sponsored by SI-BONE. Three of the authors are paid consultants to SI-BONE. One of the authors is an employee of SI-BONE.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
Miller et al. (2013)	Non-comparative, retrospective case-series Intervention: iFuse. ●	5,319 patients underwent SIJF with iFuse between April 2009 and January 2013. No baseline characteristics presented. Multi-centre (post-market surveillance of SIJF carried out in the USA and Europe). Follow-up time: database complaints between April 2009 and January 2013. No mean follow-up presented. People with SIJ disruption or degenerative sacroilitis. ●	**Relevant to scope:** Device-related events, procedure-related events, clinical events and revisions. ● **Not relevant to scope:** None.	Post-market surveillance of complaints from SIJF using iFuse showed a low number of procedure-related, device-related and clinical events. In addition, a small number of revision procedures were carried out.	None.	Data for this study were obtained from a database maintained by the manufacturer in line with the post-market surveillance mandated by the Food and Drug Administration (FDA). The study presents data on complaints and revisions only. The study was supported in part by SI-BONE. One of the study authors is an employee of SI-BONE.
Rudolf and Capobianco (2014)	Non-comparative, prospective study. Intervention: iFuse. ●	21 patients underwent SIJF with iFuse between October 2007 and March 2009. 17 patients were available for follow-up.	**Relevant to scope:** Pain and patient satisfaction at baseline, 12, 24 and 60 months, health-related	Pain scores were significantly reduced following SIJF and the low scores were maintained at 5 year follow-up. 6/8 domains from	4 patients (patient passed away n=2, lost to follow-up n=1, non-device related accident n=1).	ODI was only collected at the 5 year follow-up and therefore no comparisons between baseline and other time-points can be made. The

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		Mean (SD, range) age (years) 58 (±13.6, 36-85), 13 females (77%). Prior treatment: prior lumbar fusion n=8 (47%). Single-centre (USA). Follow-up time: 5 years. People with SIJ disruption and/or degenerative sacroilitis.	quality of life at baseline, 12 and 60 months, disability (ODI) at 60 months, adverse events, SIJ health related outcomes, radiographic evidence at 12 and 60 months. ● **Not relevant to scope:** None.	the SIJ related health outcome survey were significantly lower at baseline than 6 months. There were a small number of post-procedure related events and no revisions were required.		questionnaire used was created by the authors by combining components from the 36 item short form survey (SF-36) and ODI. It therefore has not been validated. The study is sponsored by SI-BONE. One of the authors is an SI-BONE investor, consultant and clinical trial investigator. The other author is an employee of SI-BONE. An employee of SI-BONE provided statistical advice.
Sachs et al. (2016)	Non-comparative retrospective case series. Intervention: iFuse. ●	107 patients underwent SIJF with iFuse prior to December 2012. Mean age (range) 57.5 (18.6-87), gender not presented. Prior treatment: physical therapy n=66 (61.7%),	**Relevant to scope:** SIJ pain at baseline and follow-up, ODI, patient satisfaction and	Patient pain scores were significantly lower following SIJF and patient satisfaction rates at follow-up were high. Low numbers of	None.	ODI scores at baseline were not available for the majority of patients. Therefore, baseline ODI was not presented and no comparisons between baseline and 12

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		SIJ steroid injections n=69 (64.5%), RFA of branches of sacral nerve roots n=18 (16.8%) and prior lumbar fusion n=39 (36.4%). Mean follow-up: 3.7 years (range 3-4.7) after SIJF. Multi-centre (7 centres in USA). Mean (range) follow-up: 3.7 years (3-4.7). People with SIJ dysfunction. ●	revision rates at follow-up. ● **Not relevant to scope:** Other lumbar spine or hip surgeries during follow-up. ●	procedure-related events and revisions were observed.		months could be carried out. The study was sponsored by manufacturer (SI-BONE). Two of the authors are consultants to SI-BONE. All of the authors conduct clinical research for SI-BONE-sponsored clinical trials. However, the authors report no other conflicts of interest in the study. Patients received a nominal payment for taking part in the study.
Schroeder et al. (2013)	Non-comparative, retrospective study. Intervention: iFuse. ●	6 participants enrolled SIJF mean (range) age (years): 50 (25-60), 6 females (100%) SIJF prior treatment: an anesthetic injection n=6	**Relevant to scope:** Pre and post pain score , ODI, and HRQoL,	Back VAS pain, ODI scores significantly decreased. Scoliosis Research Society Outcomes	None.	The images were reviewed only by a single reviewer. However, the authors state that the reviewer

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		(100%), physical therapy n=6 (100%), prior long spine fusion n=6 (100%). Single centre (USA). Mean (range) follow-up (months): 10.25 (4-15). Patients with SIJ pain after a long spine fusion procedure for scoliosis. ●	postoperative complications and radiographic outcomes ● **Not relevant to scope:** Leg pain. ●	Questionnaire (SRS22) scores significantly increased with the largest increases in the pain, function and patients' satisfaction. There were no complications in surgery or post-operatively.		was a fellowship trained spine surgeon. This study has a small number of patients. However, the study was included by the EAC as it presents results of SIJF in patients who have previously had spine fusion and may be of interest to the committee. .
iFuse sub-group analyses						
Capobianco and Cher (2015)	Comparative sub-group analysis of a non-comparative, prospective study (Duhon et al. 2016) Intervention: iFuse. ● Sub-groups: women with PPGP, women with no PPGP and men.	172 patients received treatment (women with PPGP n=20, women with no PPGP n=100 and men n=52). Women with PPGP: mean (SD) age (years) 43.3 (9.0). Women with no PPGP mean (SD) age (years) 52.5 (11.1). Men: mean (SD) age (years) 50.7 (11.4).	**Relevant to scope:** SIJ pain, ODI, and quality of life at baseline and 12 months, procedure time, procedure resources, adverse events and revisions. ● **Not relevant to scope:**	Patient pain scores and disability were significantly lower whilst health-related quality of life was significantly higher for all patients following SIJF. Patient satisfaction with the procedure was high across	Withdrawals from the study have been reported in Duhon et al. (2016).	This paper presents sub-group analysis of data presented by Duhon et al. (2016). The study was sponsored by SI-BONE. The two study authors are employees of SI-BONE. The sub-groups are not equal in number.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		(Women with PPGP were significantly younger than women with no PPGP and men; p=0.002). Prior treatment in women with PPGP : Physical therapy n=13 (65%), RFA n=2 (10%), steroid injections n=20 (100%) and prior lumbar fusion n=6 (30%). Prior treatment in women with no PPGP: Physical therapy n=60 (66.7%), RFA n=13 (14.4%), steroid injections n=87 (96.7%) and prior lumbar fusion n=38 (42.2%). Prior treatment in men: Physical therapy n=38 (61.3%), RFA n=12 (19.4%), steroid injections n=55 (88.7%) and prior lumbar fusion n=32 (51.6%).	None.	all groups. There was no significant difference between women with PPGP, women with no PPGP and men in terms of pain scores, disability and health-related quality of life and satisfaction following SIJF. Procedure-related events and revisions were observed in the three groups.		This study has been included as the use of iFuse in women with PPGP may be of interest to the committee.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals/ Cross-over	EAC Comments
		Multi-centre (26 sites in the USA). Follow-up time: 12 months. People with SIJ dysfunction. ●				
SRS, Scoliosis Research Society						

2.4 Overview of methodologies of all included studies

A total of twelve studies were included by the EAC. Of these, there were 2 RCTs, 3 retrospective comparative studies and 7 non-comparative studies. The comparator in both RCTs (Dengler et al. 2017b; Polly et al. 2016a) was conservative management. One of the retrospective comparative studies (Vanaclocha et al. 2018) had two comparators, these were conservative management and SID using RFA. The comparator in one retrospective comparative study (Spain and Holt 2017) was SIJ fixation using screws but this study presented a comparison of revision rates only. The remaining retrospective comparative study (Capobianco and Cher 2015) was a sub-group analysis of a non-comparative, prospective study (Duhon et al. 2016). However, this study compared outcomes between groups of participants and did not compare treatments.

In the majority of the studies (n=4) the device was used in a patient population with SIJ dysfunction. Patient populations in the remaining studies included those with SIJ disruption or degenerative sacroilitis (n=2), lower back pain originating from the SIJ (n=1), unresolved SIJ pain (n=1), SIJ syndrome (n=1) and SIJ pain after a long spine fusion procedure for scoliosis (n=1). In addition, two of the included studies contained patient populations the EAC believed would be of interest to the committee. One study included patients requiring revision surgery following SIJF and the remaining study was a sub-group analysis of SIJ pain dysfunction in women with PPGP.

The EAC considers that the evidence base for the use of iFuse is quite strong. The two RCTs present outcomes at 12 months (Dengler et al. 2017b) and 24 months (Polly et al. 2016a) for iFuse and conservative/non-surgical management. It is worth noting that in the study by Dengler et al. (2017b), patients receiving conservative management were not permitted to receive SIJ steroid injections or SID through RFA but were permitted to receive cognitive behavioural therapy (CBT), if available at their site. Conversely, patients receiving non-surgical management in the study by Polly et al. (2016a) were permitted to receive SIJ steroid injections or SID through RFA but were not offered CBT. Note that neither RCT was blinded, as surgery is

required to place the iFuse implant and conservative management does not include surgery. Although this may present a small risk of bias, the EAC considers this to be an unavoidable limitation. One retrospective comparative study presented outcomes at 6 years for iFuse versus conservative management or SID through RFA. There was a lack of comparative evidence for the use of iFuse versus SIJ fixation using screws and the single study (Spain and Holt 2017) comparing these two treatments presented revision rates only.

2.5 Overview and critique of the company's critical appraisal

The company completed critical appraisal tables according to the suggested format in the submission template (these have been adapted from the Centre for Reviews and Dissemination and the Critical Appraisal Skills Programme (CASP)).

The company has completed 4 critical appraisal tables in total. Three of the four tables have been completed for trials in their entirety, one for each trial (INSITE, iMIA and SIFI). The EAC would like to note that individual studies arising from these trials have not been critically appraised by the company.

The remaining table contains a critical appraisal of the study by Vanaclocha et al. 2018. The EAC agrees that outcomes were accurately measured through the use of a VAS for pain and ODI to measure disability. The company did not note in their critical appraisal that follow-up time differed for the treatment groups. In addition many of the patients received conservative management of their pain due to lack of insurance coverage for SIJF with iFuse or SID through RFA. Patients were not randomised to each treatment.

The EAC conducted its own critical appraisal of the 12 studies included in this assessment (Appendix C – EAC critical appraisal of included studies.). The EAC considered that on the whole the quality of the evidence was strong, particularly for comparative evidence on the use of iFuse vs. conservative/non-surgical management. However, a large number of studies were not included by the EAC due to patients being presented in other studies

and this limited the evidence on the use of iFuse compared to open surgery considerably.

2.6 Results

Results of all the included studies (n=12) are summarised below (Table 4). We have presented scope-specific data only. The case study by Palmiere et al. (2017) has been discussed in section 3.7 (Description of the adverse events).

Table 4| Outcomes from included studies.

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
iFuse vs. conservative management						
Dengler et al. (2017b) - RCT - iFuse (SIJF) vs. conservative management through optimisation of medical therapy, individualised physiotherapy and information and patient reassurance (CM) - Multi-centre - Patients with LBP originating from the SIJ.	6 months results Mean (SD) LBP improvement at 6 months vs. baseline: SIJF: 43.3 (±25), p<0.0001; CM: 5.7 (±24.4), p=0.1105. LBP improvement of ≥20 VAS points (minimal clinically important difference): SIJF: 78.8% of patients, CM: 22.4% of patients; p<0.0001).	ODI Mean (SD) ODI at baseline, 3, 6 and 12 months: SIJF: 57.5 (±14.4), 35.1 (±18.3), 32 (±18.4) and 32.1 (±19.9) CM: 55.6 (±13.7), 50.6 (±15.5), 50.2 (±17.2) and 46.9 (20.8). Mean ODI was significantly lower in the SIJF group than CM group at 12 months (p<0.0001). Function	EQ-5D Mean (SD) EQ-5D time trade-off (TTO) at baseline, 3, 6 and 12 months: SIJF: 0.35 (±0.24), 0.69 (±0.25), 0.73 (±0.24) and 0.74 (0.25) CM: 0.37 (±0.27), 0.46 (±0.29), 0.48 (±0.3) and 0.54 (±0.33). Mean EQ-5D TTO was significantly higher in the SIJF group than CM group at 12 months (p=0.0009). Mean (SD) EQ-5D VAS at baseline, 3, 6 and 12 months:	Distance walked and work status has been presented but not times.	SIJF Number of iFuse implants used: 3 implants n=51/52 patients (98%), 4 implants n=1/52 patients (2%). 17/52 patients underwent bilateral SIJF. Median procedure duration (min) (range): 54 (19 - 107) Median fluoroscopy time (min) (range): 2.1 (1.0 – 4.0) CM Interventions received during the first 6 months:	Median days (range): 3 (1 - 28)

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
	Patients achieving a 40 point, 30% or 50% improvement in VAS LBP were all significantly higher for SIJF patients than CM (p<0.0001; no values presented but shown in a figure). <u>12 months results:</u> Mean (SD) LBP improvement at 12 months: SIJF: 41.6 (±27), CM: 14 (±33.4); p<0.0001). Patients achieving a 40 point, 30% or 50%	SIJ function improvement between baseline and 6 months (measured using active straight leg raise test (ASLR): SIJF: 2 points (p<0.0001); CM: 0.2 points (p=0.3247).	SIJF: 48.1 (±19.3), 50.2 (±19.6), 49.8 (±21.6) and 53.5 (±23.8) CM: 41.1 (±21.3), 61.5 (±21.6), 62.8 (±21.5) and 64.9 (±20.9). Mean EQ-5D VAS was significantly lower in the SIJF group than CM group at 12 months (p=0.0005). <u>Depression</u> Mean (SD) Zung depression scale at baseline, 3, 6 and 12 months: SIJF: 45.7 (±9.1), 40.2 (±8.6), 40.1 (±9.8) and 39.6 (±9.2) CM: 45.4 (±8), 46.1 (±9.4), 45.4 (±8.3) and 44.4 (±9.6). Mean Zung depression scale was		Number of physical therapy sessions (%): 1: n=1 (2%); 2 to 4: n=2 (3.9%); 5 to 10: n=1 (2%); 11 to 15: n=9 (17.6%); >15: n=38 (74.5%). Number of CBT sessions (%): 0: n=27 (52.9%); 1: n=1 (2%); 2 to 5: n=7 (13.7%); 6 to 10: n=10 (19.6%); 11 to 15: n=3 (5.9%); >15: n=3 (5.9%).	

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
	improvement in VAS LBP were all significantly higher for SIJF patients than CM (p=0.0033, p=0.004 and p=0.0008 respectively); no values presented but shown in a figure).		significantly lower in the SIJF group than CM group at 12 months (p=0.0035). Patient satisfaction Number of patients "very satisfied" with the received treatment at 6 months: CM n=9 (18.4%), SIJF n=28 (53.8%); p<0.0001.			
Polly et al. (2016a) - RCT - iFuse (SIJF) vs. NSM consisting of pain medications, physical therapy, intraarticular SIJ steroid injections and RFA of lateral branches of the sacral nerve roots.	SIJF group mean SIJ pain score at baseline, 6, 12 and 24 months follow-up: 82.3, 30.1, 28.6 and 26.7 (p<0.0001). NSM group mean SIJ pain score at baseline and 6	ODI SIJF group mean ODI at baseline, 6, 12 and 24 months: 57.2, 29.9, 28.3 and 28.7 (p<0.0001). NSM group mean ODI difference between	EQ-5D SIJF mean EQ-5D TTO index improvement at 6, 12 and 24 months: 0.29, 0.31 and 0.28 points (p<0.0001). NSM mean EQ-5D TTO index improvement at 6 months: 0.06 points (p=0.1740; p<0.0001	Work status at the start of study was collected but time to return to work/normal activities was not.	SIJF Number of iFuse implants used: 2 implants n=5/102 (4.9%), 3 implants n=93/102 (91.2%), 4 implants n=4 (3.9%). 24/102 (23.5%) patients underwent bilateral SIJF. Mean procedure time (minutes) (SD, range):	Mean length of hospital stay (days) (SD, range): 0.8 (1.0, 0-7). Length of hospital stay (number of patients): 1-2 days n=57 (55.9%), ≥3 days n=3

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
- Multi-centre - Patients with chronic SIJ dysfunction.	months follow-up: 82.2 and 70.3 (no p value presented). VAS SIJ pain improvement at 6 months: 38.2 points greater for the SIJF group compared to the NSM group (p<0.0001). Patients achieving ≥20 point improvement in VAS SIJ pain at 6 months: SIJF: 84/101 (83.2%), NSM: 12/43 (27.9%) (no p value presented).	baseline and 6 months: 4.6 point decrease (p=0.0537).	for difference in change score vs. SIFJ). <u>SF-36</u> SIJF mean SF-36 physical component summary (PCS) score improvement at 6, 12 and 24 months: 12.5, 12.8 and 11.2 points (p<0.0001). NSM mean SF-36 PCS score improvement at 6 months: 3.9 points (p=0.299; p< 0.0001 for difference in change score vs. SIJF). <u>Patient satisfaction</u> 6 months: SIJF=77.2% very satisfied, NSM 27.3% very satisfied (p<0.0001).		44.9 (22.3, 14-140). Procedure time (number of patients): < 30 minutes n=30 (29.4%), 30-60 minutes n=50 (49%), >60 minutes n=22 (21.6%). <u>NSM</u> Interventions: 45/46 (97.8%) patients received physical therapy (PT). 34/46 (73.9%) underwent at least one steroid injection (6 patients underwent 2 injections). 21/46 (45.7%) underwent at least one RFA. 40/46 (87%) underwent at least two types of NSM treatments in	(2.9%), discharged same day n=42 (41.2%).

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
	Opioid use (% participants) SIJF: baseline= 68.6%, 6 months=58.4%; NSM: baseline=63.0%, 6 months=70.5%.		SIJF: 12 months=78%, 24 months=73.3%.		addition to the use of pain medications.	
Vanaclocha et al. (2018) -Comparative, retrospective study. -iFuse vs. CM, SID Single centre (Spain). -Patients with unresolved SIJ pain.	VAS score The difference in VAS at 6 months and beyond: SIJF vs. CM 6 points (p<0.001) SIJF vs. SID 4.5 points (p<0.001). Opioid use SIJF: At baseline n=17 (63%), 1 month after treatment n=4	Mean ODI difference beyond 6 months: SIJF vs. CM 24 points (p<0.001) SIJF vs. SID 17 points (p<0.001) All SIJF patients showed at least a 15-point improvement at year 4 (p<0.001 between baseline and year 4).	Not a study outcome.	Work status has been presented, but not times.	SID: average procedure time <1h SIJF: average procedure time 48 min; bilateral cases (n=3) 15 min longer.	SIJF: all patients discharged the day following surgery.

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
	(14.8%), 6 months after treatment n=2 (7.4%), last follow-up n=2 (7.4%) Last follow-up vs. baseline p=0.0003 <u>SID:</u> At baseline n=26 (55.3%), 1 month after treatment n=8 (17%), 6 months after treatment n=8 (17%), last follow-up n=40 (85.1%) Last follow-up vs. baseline p=0.0012 <u>CM:</u> At baseline n=31 (49.2%), 1					

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
	month after treatment n=27 (42.9%), 6 months after treatment n=28 (44.4%), last follow-up n=53 (84.1%) Last follow-up vs. baseline p<0.0001.					
iFuse vs. SIJ fixation with screws						
Spain and Holt (2017) - Comparative, retrospective cohort study. - iFuse vs. SIJ fixation using screws. - Single centre - People with SIJ dysfunction.	Not a study outcome	Not a study outcome	Not a study outcome	Not a study outcome	Not a study outcome	Not a study outcome
Non-comparative						

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
Bornemann et al. (2017) -Non-comparative, prospective study -iFuse (SIJF) -Single centre (Germany). -Patients with SIJ	Mean (±SD) VAS values preoperative, 1, 3, 6, 12, 24 months: 84.3 (±9.2), 40.7 (±9.2), 26.5 (±4.6), 27.7 (±4.9), 26.5 (±5.2), 27 (±6.6), respectively ($p \leq 0.001$ between baseline and 1 month; $p \leq 0.001$ between baseline and 24 months).	Mean (±SD) ODI values preoperative, 1, 3, 6, 12, 24 months: 76.8 (±7.4), 40 (±7.8), 37.6 (±7.9), 33.2 (±6), 33.1 (±5.4), 31 (±7.3), respectively ($p \leq 0.001$ between baseline and 1 month; $p \leq 0.001$ between baseline and 24 months).	Not a study outcome.	Not a study outcome.	2 patients underwent bilateral SIJF, 10 patients underwent left SIJF and 12 patients right SIJF. The radiological assessment confirmed that the implants were implanted as required.	Not a study outcome.
Cher et al. (2015) -Non-comparative, retrospective case series -iFuse	Not a study outcome.	Not a study outcome.	Not a study outcome.	Not a study outcome.	10,956 (96.2%) of patients underwent unilateral, 432 (3.8%) underwent simultaneous bilateral SIJF.	Not a study outcome.

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
-Multicentre (company maintained databases) -Patients after SIJF which required a revision surgery					Number of implants used in unilateral SIJF: 2 implants n=701/10,956 (6.4%), 3 implants n=9,545/10,956 (87.1%), 4 implants n=409/10,956 (3.73%), 5 implants n=1/10,956 (0.009%) Number of implants used in bilateral SIJF: 4 implants n=67/419 (16%), 5 implants n=15/419 (3.6%), 6 implants n=322/419 (76.8%), 7 implants n=7/419 (1.7%), 8 implants n=8/419 (1.9%)	
Duhon et al. (2016) - Non-comparative, prospective study. - iFuse (SIJF).	Pain relief Mean (SD) SIJ pain (points): Baseline = 79.8 (12.8), 1 month = 37 (26.3), 3	ODI Mean (SD) ODI (points): Baseline = 55.2 (11.5), 1 month = 42.6 (17.4), 3	EQ-5D Mean (SD) EQ-5D index: Baseline = 0.43 (0.18), 6 months = 0.69 (0.21), 12	Work status at baseline, 1, 3, 6, 12, 18 and 24 months has been	Number of implants used per patient: 2 implants n=6/172 (3.5%), 3 implants n=144/172 (83.7%)	Mean (range) length of hospital stay (days): 0.79 (0-7).

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
- Multi-centre. - People with SIJ dysfunction.	months = 30.7 (25.9), 6 months = 30 (26.5), 12 months = 30.4 (27.6) 18 months = 28.1 (27.8) and 24 months = 26 (26.7); p<0.0001 between baseline and 24 months. VAS joint pain improvement ≥20 points at 6, months = 82.2%; 12 months = 81.8%; and 24 months = 83.9%. <u>Medication use</u>	months = 33.8 (18.8), 6 months = 32.5 (19.7), 12 months = 31.5 (19.2) and 24 months = 30.9 (20.5); p<0.0001 between baseline and 24 months.	months = 0.71 (0.2) and 24 months = 0.71 (0.22); p<0.0001 between baseline and 24 months. <u>SF-36</u> Mean (SD) SF-36 PCS: Baseline = 31.7 (5.6), 6 months = 40.1 (9.6), 12 months = 40.5 (9.6) and 24 months = 40.7 (10.3); p<0.0001 between baseline and 24 months. Mean (SD) SF-36 mental component summary (MCS): Baseline = 38.5 (11.3), 6 months = 47.8 (11.6), 12 months = 48.2 (12.3) and 49 (11.5); p<0.0001 between	presented in a figure. However, time to return to work was not a study outcome.	and 4 implants n=22 (12.8%). 14/172 (8.1%) patients underwent bilateral SIJF. Mean (SD, range) procedure time (minutes): 46.6 (16.1, 13-111). <u>Radiographic evidence of union</u> Twelve month CT in 159/161 patients (98.8%) still participating at month 12: Bone adherent/ adjacent to >30% of the surface area of the implant was observed in >90% of implants. Bony apposition to at least 30% of the	164/172 (95.3%) were discharged on the same day or within 2 days.

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
	Opioid use at baseline and 25 months: 76.2% and 55% respectively.		baseline and 24 months. Patient satisfaction 24 months: 78.1% patients very satisfied, 93.8% patients very or somewhat satisfied.		implant surface area on both iliac and sacral sides of ≥2 implants: 97% of treated sides.	
Miller et al. (2013) - Non-comparative, retrospective study (post-market surveillance of complaints) - iFuse (SIJF) - Multi-centre - People with SIJ disruption or degenerative sacroiliitis.	Not a study outcome.	Not a study outcome.	Not a study outcome.	Not a study outcome.	Not a study outcome.	Not a study outcome.
Rudolf and Capobianco (2014)	VAS pain Mean (SD) VAS pain at baseline,	ODI Mean (SD) ODI at 5 years:	SIJ-related health outcomes survey	Not a study outcome.	1 patient (6%) underwent bilateral, 16 patients (94%)	Not a study outcome.

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
- Non-comparative, prospective study - iFuse (SIJF) - Single-centre (USA)	12, 24 and 60 months: 8.3 (±1.4), 3.4 (±2.4), 1.4 (±2.6), 2.4 (±2.2). Scores at 12, 24 and 60 months are significantly lower than baseline (p<0.0001). Number of patients reaching pain VAS MCID at 12, 24 and 60 months: 13 (76.5%).14 (82.4%), 15 (88.2%).	21.5 (±22.7).	Mean scores (SD) at baseline, 12 and 60 months for domains in the survey (p-values are comparisons between baseline and 60 months): Light activities = 6.4 (±2.3), 3 (±1.9), 2.4 (±2.0); p<0.001 Moderate activities = 8.2 (±2.7), 5.1 (±3.3), 4.4 (±3.5); p<0.001 Vigorous activities = 9.6 (±0.8), 6.6 (±3.7), 4.8 (±3.5); p<0.001 Sleep = 7.5 (±2.0), 3.6 (±3.1), 3.3 (±3.3); p<0.001 Lifting = 5.5 (±3.0), 5.9 (±3.2), 4.6 (±3.3); p=0.45 Overall happiness = 6.4 (±2.8), 3.2, (±1.9), 3.8 (±2.4); p=0.02		underwent unilateral SIJF. Mean (SD, range) procedure time (minutes): 65 (18, 43-110).	

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
			Social interest = 4.2 (±2.7), 4.9 (±3.2), 3.9 (±2.7); p=0.81 Pain affect on social interest = 7.2 (±2.3), 2.6 (±2.1), 3.1 (±2.7); p<0.001.			
Sachs et al. (2016) - Non-comparative retrospective case series. - iFuse (SIJF) - Multi-centre - People with SIJ dysfunction.	Pain relief Mean (SD) SIJ pain (points): Baseline = 7.5 (1.7) and at follow-up = 2.6 (2.7); p<0.0001.	ODI Mean (SD) ODI (points): At follow-up: 28.2 (21.3).	Patient satisfaction Satisfaction rate at follow up: 67.3% very satisfied, 20.6% somewhat satisfied.	Results presented on whether patients' working status improved compared to baseline but no time to return to work/normal activities was presented.	Not a study outcome.	Not a study outcome.
Schroeder et al. (2013)	Mean (minimal clinically important difference (MCID)	Mean (MCID according to the study) ODI scores pre- to post-operative:	Mean (MCID according to the study) SRS22 scores pre- to post-operative:	Not a study outcome.	4 patients underwent bilateral SIJF, 1 patient underwent left SIJF and 1 patient underwent right SIJF.	Mean (range) length of stay (days): 2 (1 - 4).

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
-Non-comparative, retrospective case series -iFuse -Single centre (USA). -Patients with SIJ after a long spine fusion for scoliosis.	according to the study) back VAS pre- to post-operative: 7.83 to 2.67 (1.2); p<0.005.	22.2 to 10.5 (12.4); p=0.0005.	2.93 to 3.65 (0.2); p=0.035.		Bony bridging (successful fusion) could be seen in 4/6 patients at the time of their last follow-up.	
iFuse sub-group analyses						
Capobianco and Cher (2015) - Comparative sub-group analysis of data presented by Duhon et al. (2015). - iFuse (SIJF) - Multi-centre - Sub-groups: women with PPGP, women with no PPGP and men.	SIJ pain Mean (SD) VAS SI pain at baseline, 1, 3, 6 and 12 months: Women with PPGP = 81.9 (10.0), 31.6 (25.3), 36 (24.4), 21.3 (17.6), 31.4 (30.9); p<0.0001 between baseline and 12 months.	ODI Mean (SD) ODI at baseline, 1, 3, 6 and 12 months: Women with PPGP = 52.2 (12.7), 43 (16.9), 37.6 (17.3), 30.4 (20), 32.8 (21.4); p<0.0001 between baseline and 12 months.	SF-36 Mean (SD) SF-36 PCS at baseline, 6 and 12 months: Women with PPGP = 32 (5.6), 40 (11.1), 41.6 (10.8); p<0.0001 between baseline and 12 months. Women with no PPGP = 31.1 (5.6), 40.5 (9.2), 40 (9.6); p<0.0001 between baseline and 12 months.	Not a study outcome.	Mean (SD) procedure time (minutes): 46.4 (16.1).	Mean (SD, range) length of hospital stay (days): 0.8 (0.97, 0-7). Length of hospital stay (number of patients): discharged same day n=69 (40.1%).

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
- People with SIJ dysfunction	Women with no PPGP = 79.9 (13.3), 38.9 (26.7), 29.6 (26.3), 31.5 (27), 32.7 (28.5); p<0.001 between baseline and 12 months. Men = 78.9 (12.9), 35.2 (26.2), 30.6 (26), 30.2 (28), 25 (24.0); p<0.0001 between baseline and 12 months. There was no significant difference at 12 months between groups.	Women with no PPGP = 55 (11.2), 44.5 (16.9), 33.1 (17.8), 31 (18.7), 30.8 (19.1); p<0.0001 between baseline and 12 months. Men = 56.7 (11.5), 38.8 (18.3), 33.8 (21.2), 36.4 (21.4), 31.9 (18.9); p<0.0001 between baseline and 12 months. There was no significant difference at 12 months between groups.	Men = 32.7 (5.5), 39.8 (10.1), 40.5 (8.9); p<0.0001 between baseline and 12 months. Mean (SD) SF-36 MCS at baseline, 6 and 12 months: Women with PPGP = 42.2 (12.4), 49.7 (9.6), 49 (10.8); p<0.0001 between baseline and 12 months. Women with no PPGP = 37.7 (11.6), 48.8 (10.8), 47.7 (12.9); p<0.0001 between baseline and 12 months. Men = 38.6 (10.3), 45.1 (13.2), 18 (12.1); p<0.0001 between baseline and 12 months. <u>EQ-5D</u>			1 day n=85 (49.4%), 2 days n=10 (5.8%), ≥3 days n= 8 (4.7%),

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
			Mean (SD) EQ-5D index at baseline, 6 and 12 months: Women with PPGP = 0.42 (0.14), 0.72 (0.23), 0.72 (0.21); p< 0.0001 between baseline and 12 months. Women with no PPGP = 0.43 (0.18), 0.7 (0.19), 0.7 (0.2); p<0.0001. Men = 0.45 (0.19), 0.64 (0.25), 0.72 (0.19); p<0.0001 between baseline and 12 months. There was no significant difference in SF-36 or EQ-5D at 12 months between groups. <u>Patient satisfaction</u>			

Study	Back/SI joint pain relief (including medication use)	Improvement in function and disability from back pain	Patient HRQoL and satisfaction	Time to return to work/normal activities	Procedure time, resources and radiographic evidence of union	Length of hospital stay
			Patients very or somewhat satisfied at 12 months: Women with PPGP n = 17 (100%), women with no PPGP n = 79 (84.0%) and men n = 42 (91.3%). There was no significant difference in patient satisfaction at 12 months between groups.			

2.7 Description of the adverse events

Details of withdrawals have been presented in Table 4. Blood loss during surgery, device-related events, postoperative complication and revision rates have been presented in Table 6. A total of 10/12 studies reported adverse events.

The majority of studies reporting revision rates for iFuse do not state when the revision was carried out. However, a study by Cher et al. (2015) states that 24% of revision surgeries occurred within the first month and that 63% occurred within the first 12 months following initial SIJF.

The company did not carry out a search to identify any Medicines and Healthcare products Regulatory Agency (MHRA) field safety notices. However, the company presented a table of adverse events it had reported to the FDA Manufacturer and User Facility Device Experience (MAUDE) database from 2008 through September 2017 in line with its reporting practices for medical device reports. There were a total of 661 adverse events reported (Table 5). The EAC carried out its own search of the FDA MAUDE database and identified a total of 652 adverse events during the same time period. The EAC acknowledges that the company is likely to identify a higher number of adverse events due to its reporting practices for medical device reports.

During its literature searching the EAC identified a case report by Palmiere et al. (2017) from Switzerland. The authors report on a fatal haemorrhage following SIJF using iFuse in a male. An autopsy of the individual highlighted a perforation of a branch of the right internal iliac artery and a potentially toxic blood tramadol concentration which was considered to have contributed to the death. The authors speculate that the drill used during the procedure pushed a guide pin into the vessels and caused a perforation. The authors believed this would be an unexpected complication and would not have been noticed during surgery.

Table 5| Adverse events reported by the company to the FDA MAUDE database from 2008-September 2017.

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

Table 6| Adverse events and complications from included studies

Study	Blood loss during surgery	Peri-operative morbidity and device-related adverse events	Postoperative infection or complications	Reoperation/ revision rates
iFuse vs. conservative management				
Dengler et al. (2017) 103 patients randomised (SIJF n=52; CM n=51).	Not a study outcome.	Device/treatment-related adverse events SIJF: 4 patients (recurrent SIJ pain attributed to device loosening in the sacrum n=2, postoperative new onset leg pain related to implant malposition n=1, postoperative haematoma n=1). CM: 0. Cross-over (received SIJF after 6 months of CM as they did not feel a benefit from CM): 2 patients (SIJ pain attributed to device loosening n=1, postoperative haematoma n=1).	None reported.	Revisions: n=2.
Polly et al. (2016a) 148 patients received their allocated treatment (SIJF n=102; NSM n=46).	Mean blood loss (cc) (SD, range): 32.7 (32.8, 0.5-250) Estimated blood loss (cc) (number of patients):	Device/treatment-related adverse events SIJF: 22 events (neuropathic symptoms n=1, urinary retention n=1, nausea/vomiting n=2, atrial fibrillation n=1, ipsilateral or contralateral SIJ pain and trochanteric bursitis	Postoperative infection SIJF: 1 patient.	SIJF: n=3 Cross-over: n=1.

Study	Blood loss during surgery	Peri-operative morbidity and device-related adverse events	Postoperative infection or complications	Reoperation/ revision rates
	0-50 n=92 (90.2%), 50-100 n=9 (8.8%), >100 n=1 (1%).	n=9, drainage n=1, haematoma n=1, infection n=1, stitch abscess n=1, delayed wound healing n=1, iliac fracture n=1, asymptomatic physical exam or radiographic findings n=2). CM: 5 events (increased SIJ pain n=1, SIJ pain due to PT n=1, back pain due to PT n=1, SIJ pain related to a steroid injection n=1, flushing and shortness of breath related to SIJ steroid injection n=1).		
Vanaclocha et al. (2018) SIJF n=27, CM n=74, SID n=51.	Not a study outcome.	SIJF: temporary postoperative sciatic pain n=2	SIJF: no complications reported.	SIJF: no revisions required.
iFuse vs. SIJ fixation with screws				
Spain and Holt (2017) 292 patients (SIJ fixation with screws n=29, SIJF with iFuse n=263).	Not a study outcome.	Not a study outcome.	Not a study outcome.	SIJF: 12 revisions in 274 patients. SIJ fixation with screws: 19 revisions in 38 patients. Cumulative probability of revision at 4 years:

Study	Blood loss during surgery	Peri-operative morbidity and device-related adverse events	Postoperative infection or complications	Reoperation/ revision rates
				SIJF=5.7%, SIJ fixation with screws=30.8% (p<0.0001).
Non-comparative				
Bornemann et al. (2017) 24 participants enrolled	Not a study outcome.	No device or surgery related adverse events.	No postoperative infections or complications.	Not a study outcome
Cher et al. (2015) 11,388 patients with a total of 11,280 sides treated.	Not a study outcome.	Not a study outcome.	Not a study outcome.	Revision after SIJF: n=315 (24% of revision surgeries occurred in the first month, 63% occurred within the first 12 months) The 4-year survival rate free from revision surgery: 96.4%. The 4-year revision rate: 3.6%. 1-year revision rates (2009-2014): 9.7%, 4.9%, 2.0%, 1.8%, 1.5% and 1.4% (p<0.0001). The 4-year probability of revision due to symptomatic

Study	Blood loss during surgery	Peri-operative morbidity and device-related adverse events	Postoperative infection or complications	Reoperation/ revision rates
				malposition was 1%, due to recurrence of symptoms – 1.94%. Reasons for revision after SIJF: symptomatic malposition n=121/315 (38.4%), recurrence of symptoms n=150/315 (47.6%), never improved symptoms n=29/215 (9.2%), fracture of ilium n=3/315 (1%), early revision for asymptomatic implant malposition n=12/315 (3.8%). 86.8% of symptomatic malposition occurred within the first 6 months. 87.9% of recurrence of symptoms occurred after month 6.
Duhon et al. (2016)	Mean (SD, range) blood loss (cc):	Device-related adverse events	Procedure related events	Revisions: n=8.

Study	Blood loss during surgery	Peri-operative morbidity and device-related adverse events	Postoperative infection or complications	Reoperation/ revision rates
194 patients enrolled. 172 patients received treatment.	51.0 (75.8, 5-800).	7 events (neuropathic pain related to device malposition n=3, SI joint or buttock pain n=2, SI joint pain after fall associated with inadequate device placement n=1 and hip pain related to periosteal bone growth around implant n=1).	26 events (buttock pain n=2, foot weakness related to anaesthesia n=1, iFuse impingement n=3, nausea/vomiting n=3, SIJ pain n=5, SI joint pain (inadequate stabilisation) n=3, urinary retention n=1, vascular injury n=1, wound drainage/irritation/infection n=6 and wound numbness n=1).	
Miller et al. (2013) 5,319 patients	Not a study outcome	204/5319 (3.8%) of patients had complaints. <u>Device-related adverse events</u> 74 events (pin bind/bend/break n=43, pin advancement n=14, radiographic halo n=13 and migration n=4).	<u>Procedure-related events</u> 108 events (improper device placement n=72 and improper device size n=36) Clinical events 140 events (any pain n=119, haematoma/excessive bleeding n=11, iliac fracture n=4, superficial wound infection n=3,	Revisions: n=96.

Study	Blood loss during surgery	Peri-operative morbidity and device-related adverse events	Postoperative infection or complications	Reoperation/ revision rates
			deep venous thrombosis n=2, deep wound infection n=1).	
Rudolf and Capobianco (2014) 21 patients, 17 available for follow-up.	Not a study outcome.	Not a study outcome.	Procedure-related events 4 events (haematoma n=1, cellulitis n=2, deep infection secondary to diverticulitis n=1).	No revisions.
Sachs et al. (2016) 107 participants	Not a study outcome.	Not a study outcome.	Procedure-related events 3 events (postoperative mild ileus n=1, suture material extending from the wound n=1, adhesive tape allergic reaction n=1).	Revisions: 5/107 (4.67%).
Schroeder et al (2013) 6 participants	Not a study outcome.	No complications.	No complications.	Not a study outcome.
iFuse sub-group analyses				
Capobianco and Cher (2015) 172 patients received treatment (women with PPGP n=20, women with	Mean (SD) blood loss (cc): 51 (76).	Presented under procedure-related events.	Procedure-related events 21 events. Women with PPGP = 4 events (wound	Revisions: 4/172 Women with PPGP: n=1

Study	Blood loss during surgery	Peri-operative morbidity and device-related adverse events	Postoperative infection or complications	Reoperation/ revision rates
no PPGP n=100 and men n=52).			infection n=2, numbness around surgical wound n=1, fall causing SIJ pain n=1). Women with no PPGP = 10 events (buttock pain n=2, postoperative neuropathy n=1, postoperative nausea/vomiting n=3, intraoperative hemorrhage n=1, neuropathy after contralateral SIJF revision n=1, urinary retention n=1, wound drainage n=1). Men = 7 events (wound infection n=2, buttock pain n=1, postoperative neuropathy n=1, SIJ pain n=2, staple irritation n=1).	Women with no PPGP: n=2 Men: n=1

2.8 Description and critique of evidence synthesis and meta-analysis

The company presented the results of a pooled analysis of the INSITE, iMIA and SIFI studies (Dengler et al. 2017a). The study presented a pooled analysis of outcomes from the three studies and also presented predictors of outcomes following SIJF with iFuse and conservative management. The paper showed a significantly larger reduction in pain scores (37.9 points, [95% CI 32.5-43.4]; p<0.0001), a significantly larger ODI improvement (18.3 points, [95% CI 14.3-22.4]; p<0.0001) and a larger improvement EQ-5D index (0.24 points, [95% CI 0.17-0.3]; p<0.0001) following SIJF than NSM. However, the EAC excluded this study as the individual studies presented the results in a clearer manner. The pooled analysis does not indicate which time-points from each study were pooled and heterogeneity between studies has not been addressed. Furthermore, the treatments permitted in the CM arm of the study by Dengler et al. (2017b) differ from those permitted in the NSM arm of the study by Polly et al. (2016). For these reasons the EAC did not carry out a meta-analysis and feels the results from the individual studies should be considered instead (Table 4).

The company also carried out a systematic review with graphical analysis. However, no details have been provided on how the company conducted their systematic review. For their graphical analysis the company plotted VAS pain scores from a total of 13 studies against time (Figure 1). This analysis was non-comparative and therefore presented pain improvement following SIJF with iFuse only. In addition, as previously discussed in section 2.3 (Included and excluded studies), the graph contains studies where patients overlap.

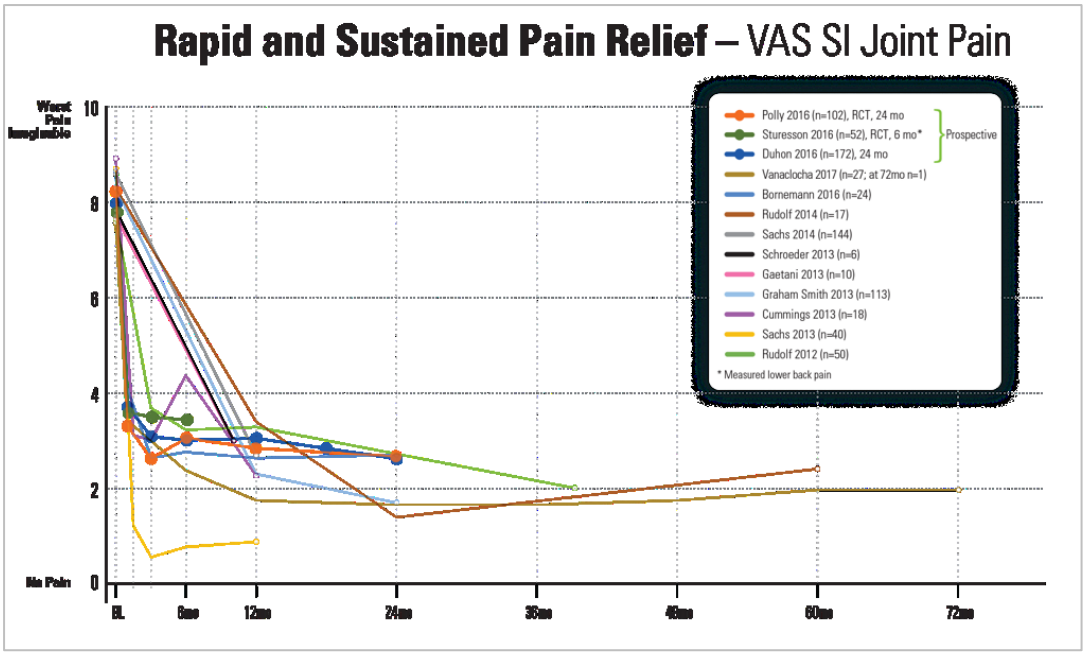

Figure 1| Company's graphical analysis of VAS SIJ pain

2.9 Ongoing studies

The company provided the details of two ongoing studies and the EAC's own search identified the same two studies (Table 7). The LOIS study presents long-term results from the previously published INSITE trial (insert link to clinical trials.gov here) and SIFI (insert link to clinical trials.gov here) study, both of which were completed in 2017. The Study of Bone Growth in the Sacroiliac Joint After Minimally Invasive Surgery With Titanium Implants (SALLY) study is a non-comparative study of SI-BONE's iFuse 3-D implant.

Table 7| Company identified ongoing studies

ID number	Description	Status
NCT02270203	Long-term follow-up in INSITE/SIFI (LOIS) is a long-term follow-up (5 years post-procedure) of patients enrolled in the INSITE trial and SIFI study. Study director: Daniel Cher (SI-BONE, Inc). Setting: multi-centre (USA). Sponsored by SI-BONE, Inc.	Active, not recruiting. Study start date: October 2014. Estimated primary completion date: December 2019. Estimated study completion date: December 2019.
NCT03122899	Study of bone growth in the sacroiliac joint after minimally invasive surgery with titanium implants (SALLY) is a non-comparative study of minimally	Recruiting. Study start date: 03/10/17. Estimated primary completion date: October 2020.

	invasive sacroiliac joint fusion surgery with iFuse-3D. Primary radiographic outcome: Bone adherence. Primary clinical outcome: disability due to low back pain (measured through ODI). Study director: Daniel Cher (SI-BONE, Inc). Setting: multi-centre (USA). Sponsored by SI-BONE, Inc.	Estimated study completion date: January 2025.

3 Economic evidence

3.1 Published economic evidence

Critique of the company's search strategy

The company's search strategy was limited to the term "economic" and "sacroiliac" which were combined with logical AND. This does not produce a sensitive search. Cedar designed a more sensitive strategy (Appendix A - Company and EAC literature search strategies and PRISMA diagrams). The company only searched the Pubmed database and did not search the full list of NICE's recommended databases. The EAC expanded the search to other databases using a more sensitive search strategy.

Critique of the company's study selection

The company found a small number of economic studies with their limited search. They excluded papers not dealing with the sacro-iliac joint, or where the intervention was another type of SI joint treatment. The Company did not appear to apply the PICO from the scope in selecting studies.

Included and excluded studies

The Savoss et al. (2016) paper included by the company considers worker productivity of patients from the societal perspective and therefore does not match the scope. The EAC excluded this paper.

Polly et al. (2016b) models the diagnostic work-up of chronic back pain and is therefore outside the scope. The EAC excluded this paper.

The other 3 papers selected by the company were from the US payer perspective and were therefore outside the scope. All of the 3 papers were sponsored by SI Bone Inc. and compared minimally invasive surgery with non-operative care (Ackerman et al. 2013, Ackerman et al. 2014 and Cher et al. 2016). The EAC excluded these papers as evidence, however they are useful in terms of external validation of the submitted model.

None of the papers included open surgery as a comparator.

Overview of methodologies of all included economic studies

Ackerman et al. (2013) and Ackerman et al. (2014) are similar models, but taken from the perspective of US Medicare and US third party payer respectively. Much of the focus of these papers is specific to these non-UK perspectives, including choices such as the time horizon being determined by conventions for presenting economic models from these perspectives. For both models, the non-surgical arm costs are calculated using databases of collected patient costs. The surgical arms use clinical opinion plus published reference costs. No mortality rates are used in either model.

Ackerman et al. (2013) presents a Medicare perspective and is described as a lifetime perspective, but appears to be a 15 year time horizon. No mortality rate modelling is described. The average age is 70 years in year 1 of the model. Ackerman et al. (2014) presents a third party payer perspective with a 3 year time horizon. Non-surgical arm costs are taken from health insurance databases. The average age at the model start was 42.5 years. Cher et al. (2016) also takes from a US third party payer perspective, but over a 5 year time period. This model does not include the cost of pain management medication in either arm, an assumption likely to favour non-surgical treatment as this relies on pain management medication. The authors also assume that the cost of providing non-surgical care reduces by 50% after the first 6 months of treatment reducing the cost of providing this treatment. Both of these assumptions are likely to reduce the calculated costs for non-surgical treatment.

Overview and critique of the company's critical appraisal for each study

The company did not carry out critical appraisal of the included economic studies.

Does the company's review of economic evidence draw conclusions from the data available?

The company concludes that the 5 studies they included in their literature review do not address the decision problem comparing iFuse implant system to all relevant comparators from an NHS payer perspective. The EAC agree

that they do not add directly to the economic evidence. They are discussed further in section 9.8 of the company submission, and in the EAC assessment report as comparative models that contribute to external model validation.

3.2 Company de novo cost analysis

Patients

The company's de novo model included patients diagnosed with chronic SIJ pain who have been unsuccessfully treated with conservative management and continue to live with chronic pain. This is slightly different wording compared with the scope which refers to people with unresolved sacroiliac joint dysfunction. Sub-groups such as women of reproductive age and patients with previous lumbar surgery were not considered separately. Unilateral versus bilateral joint implants were not considered separately as the Company was advised by clinical experts that for patients with a bilateral condition, the procedures are almost always undertaken separately.

It may not be appropriate to completely separate bilateral procedures, as with a model over a long time horizon, both procedures would be likely to be included even where performed separately.

Technology

The technology is the iFuse implant system as described in the scope.

Comparator(s)

The first comparator modelled by the company is open SIJ fusion surgery using screw or cage systems and this matches the scope. The open surgery approach is assumed to be split 50:50 into anterior or posterior. The model does not include the lateral approach as described in NICE IPG578 Minimally invasive sacroiliac joint fusion surgery for chronic sacroiliac pain.

The company has chosen to model the non-surgical pathway as a stepped pathway which includes steroid injection, RF ablation and opioid medical therapy. Physical therapy is not included in the model as it was assumed to

be offered prior to any of the treatment options and is therefore not considered by the company to be a comparator.

There is no consideration of optimisation of medical therapy, or of individualised psychological and physical therapy with provision of adequate information and reassurance as described in the scope.

Model structure

The model structure for open surgery versus iFuse implant is simple (Figure 2), and a reasonable representation of a patient pathway in the NHS for this comparator. Experts noted that open surgery is not widely used. All patients receive surgery which may result in a good response (described in model as mild pain) or chronic pain. From either of these states there is an equal risk of requiring revision. All patients that enter the revision state move back to good response or chronic pain in the next model cycle. The risk of revision is constant over time and is the same for patients who have already received revision surgery. Mild pain is assumed to require no further treatment unless the patient has revision surgery.

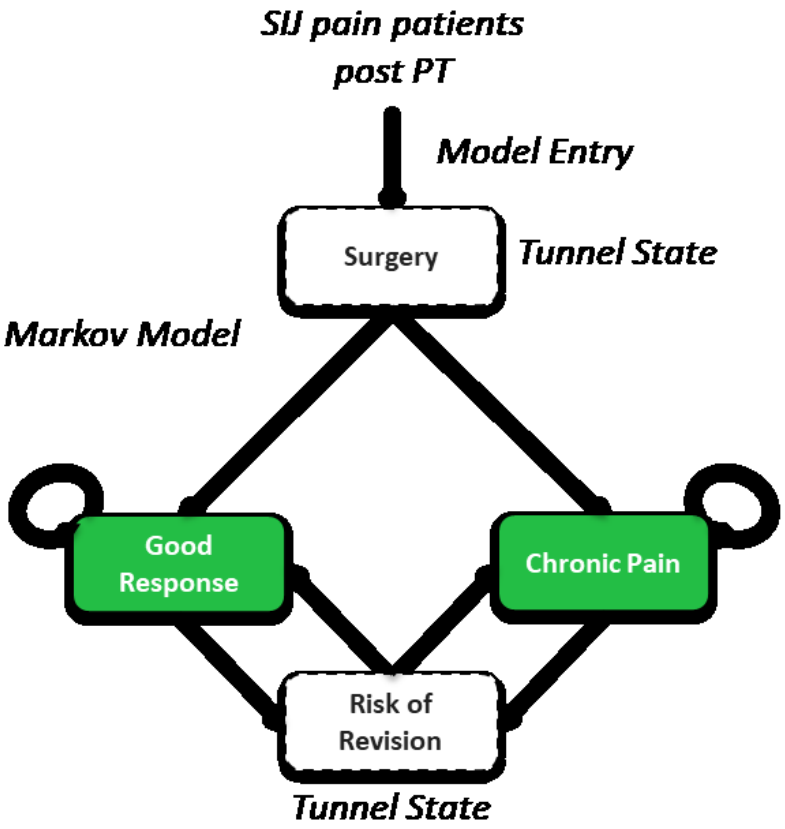

Figure 2| Company's submitted model for open surgery (SIJ fixation with screws or cage systems) vs. iFuse.

For the stepped pathway, all patients enter the model receiving their first steroid injection. They may move into a chronic pain state or a recurrent steroid injections state. Chronic pain is a final state, patients do not move from this to any future treatment. From recurrent steroid injections they may progress to the first RF ablation. This may lead to chronic pain or recurrent RF ablation. In both the chronic pain states, patients are receiving medical therapy, which is assumed to be an opioid pain management regimen, and no longer receive any other therapies. For the stepped pathway, there is no equivalent state to "mild pain" that requires no further treatment. Patients are either in chronic pain requiring opioids, or are receiving steroid injections or radiofrequency ablations. Patients cannot get better permanently in this model (Figure 3). Overall this appears to be a reasonable representation of a non-surgical patient pathway, although there will be many variations in local

practice. However expert opinion was that in practice that patients will be offered steroid injections before iFUSE, and where non-surgical management is unsuccessful a surgical option such as iFUSE would be offered.

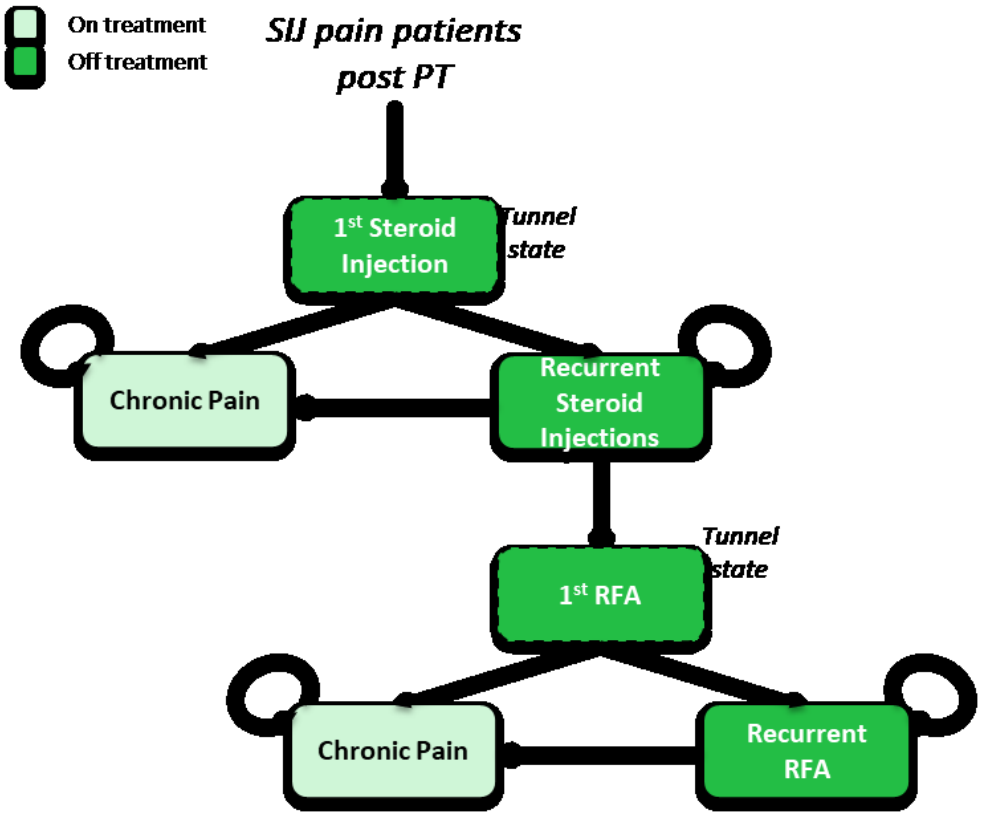

Figure 3| Company's submitted model for a stepped pathway of non-surgical care vs. iFuse.

Summary of the base case

Table 8| Company's base case results

	Total per patient cost (£)	Base case difference (£)	Lowest estimate (£)	Highest estimate (£)
iFuse	£7,318.99			
Open surgery	£11,591.85	-£4,272.86	-£2,919.59	-£7,545.17
Stepped pathway	£7,644.06	-£325.07	+£2,219.58	-£3,828.45

Clinical parameters and variables

The company used a 7 year time horizon for their model. There is no death state in the model, and patients continue to incur costs for the full 7 years. Although it could be included, the mean age of patients in the studies was in their 50s, so adjustment over 7 years is likely to be minimal. A longer time horizon would require an adjustment for general survival, however there is limited follow-up data beyond the first 4 years. A longer time horizon is not justified as there is insufficient information on variables such as the long term revision rate. iFuse becomes cost saving compared with open surgery in year 1 of the base case model. The stepped pathway is cost incurring up to 6 years and then becomes cost saving at 7 years. The time horizon chosen for the model is 7 years.

The company identified a large number of assumptions underlying the model (Table 9).

Table 9| Assumptions made by the company which underlie their models and EAC comments on the assumptions.

Aspect	Assumption	Company Rationale	EAC comment
iFuse vs. open surgery			
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.	The EAC sought expert opinion and it was stated that posterior surgery would be carried out more frequently than anterior open surgery. However, expert opinion also stated they feel that very few people would use an open surgical technique now. Although this is an important variable in the deterministic sensitivity analysis, a probability of 0-100% was investigated and iFuse remains cost saving.
Surgery response	Patients with a good response post-surgery remain in this health state for the duration of the model unless they	[redacted]	3 year results from the LOIS study were [redacted]

	have a revision surgery.	[redacted]	[redacted]
	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 iFuse and open surgery.	This assumption was applied as data were 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 however the impact of this is expected to be minimal as revision surgeries following MIS with the iFuse Implant System are rare.	This assumption was not applied in the same way to both arms. For iFuse, 50% of revision patients have a good outcome. For open surgery, 27% of revision patients have a good outcome. Instead of taking 50% of all patients undergoing revision, the model uses 50% of the probability of having a good outcome after primary surgery.
	Patients with a "good response" do not require any pain medication at all.	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.	Any cost increase would favour comparators, as more patients stay in the "good response category for iFuse.
Surgery revisions costs	The cost of revision surgery is assumed to be the same as the original surgical	This assumption was applied as no data was available for the procedure times and	This is likely to favour the comparator, unless revisions using iFuse are more complicated than

	procedure minus the training costs and the cost of early revision.	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 (open surgery) as the revision rates with open surgery are considerably higher compared to iFuse.	when using open surgical techniques. The impact is not likely to be large due to the small number of revisions observed.
Risk of revision surgery	Risk of revision is constant. It does not vary with time and is not dependant on any previous revision surgeries.	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	Although this may not be clinically accurate, given the low revision rate for both arms in the model it is unlikely to change the result by a large amount. Expert opinion states that revision surgery for iFuse is sometimes required but would be earlier rather than later.

		expected to bias the results as this same approach was applied in both arms.	
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.	It is assumed that patients with a good response (described as mild pain in the model) do not require any pain medication. Expert opinion on this assumption was sought by the EAC. Clinical experts stated that temporary pain relive may be required during recovery for the first few weeks. However, following successful surgery they would not expect a patient to require any prescribed pain medication. The low cost scenario includes lower cost drug regimen plus GP visit The high cost scenario includes higher cost drug regimen plus GP and outpatient visit.
	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	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	The calculation used is described in the assumptions above.

	pain management consultant every six-months to review their medication regimen.	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.	
iFuse vs. stepped pathway			
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 stepped pathway 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.	The EAC sought expert advice for the assumption of pain relief from a steroid injection. One clinical expert acknowledged that steroid injections are carried out at ~6 month intervals.
	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 stepped pathway as it is likely that some patients may also be prescribed an opioid based regimen while on repeated steroid injections.	The EAC agrees that this assumption is conservative and will favour the comparator.

The EAC identified further assumptions used by the company in their submitted model (Table 10).

Table 10| Additional assumptions identified by the EAC

Assumption	EAC comment
All patients are alive for the duration of the 7 year model.	No death state in model. This has minimal impact for the population in question, and when using a 7 year time horizon.
The cost of adverse events is entirely captured in length of hospital stay.	Any adverse events requiring re-admission would not be captured.
Physical therapy is not included in the model.	The company argues that it is included prior to treatment for both arms. The EAC sought expert opinion on whether physical therapy is required following surgery. Patients will receive physical therapy following their surgery. However, according to expert opinion this is not standardised and each physiotherapist will have their own preference for the number of sessions a patient will receive. This was not included in the model. The EAC considers that this would be required for both iFuse and open surgery and therefore any impact on cost savings would be negligible. The difference between iFuse and the stepped pathway may be important and may lead to a longer time horizon before iFuse becomes cost saving.
The model structure and use of surgery as a tunnel state means that patients do not arrive in mild or severe pain states for 6 months, and fewer revisions occur in the first year.	Cher et al. (2015) was used for the iFuse probability of revision, but reported that 63% of the revisions occurred in the first year post surgery. The cumulative revision rates occur one year later in the model than in the data than they are based on, although revision costs for the first 6 months are included in the initial surgery costs. If this were corrected it would be likely to shift surgical revision costs to the start of the model, and increase overall costs as more patients would move to the chronic pain state earlier. The cost increase would be greater for the open surgery arm, since the revision rate is greater.
Patients on the stepped pathway who move into chronic pain state would not be considered for further therapy, and would	The majority of patients (92%) in this arm are in the chronic pain arm at the end of 7 years.

remain in the chronic pain state for the rest of the model duration	
Probability of continuing with either steroid injections or ablation is constant over time.	The EAC sought expert opinion on this. It was the opinion of a clinical expert that if steroid injections are successful but only temporary a point would come to stop and consider surgery. The expert also stated that a small number of patients would receive radiofrequency ablation as the evidence does not support its use. The assumption is therefore not accurate as patients would likely have surgery if they received no benefit from steroid injections or radiofrequency ablation.

The company commissioned independent interviews of 2 pain management consultants and 2 surgical consultants. The interviews were used to validate clinical parameters obtained from the literature, the care pathway in the model and to obtain assumptions for response rates for steroid injections and RF ablation.

The length of hospital stay for open surgery is set at 8 days and 2 references are given in Table C5 of the company submission, Ledonio et al. (2014a) and Nystrom et. al. (2017). Nystrom et al. (2017) gives a mean length of stay 8 days, but Ledonio et al. (2014a) has a mean length of stay of 3.3 days. Neither study was included by the EAC in the clinical evidence, however as there were no alternative data the EAC used a weighted average (Table 11). Choosing the 8 day length of stay tends to favour iFuse. The selection was justified by the company by being a larger and more recent study.

The length of stay of 1.7 days for iFuse was taken from a poor quality review (Heiney et al. 2015). As there was significant heterogeneity reported in the study, the EAC chose to use data reported in its included studies. Four studies reported mean length of hospital stay and these were used in the EAC's analysis of the model. One study, Dengler et al. 2017b, reported median length of stay as 3 days (range 1-28 days) but did not include sufficient information to calculate the mean. One study, Vanaclocha et al. (2018), reported that all patients were discharged the day following surgery.

The company's model includes two rates for good response to treatment variables, one for iFuse and one for open surgery. The values both were obtained from a review (Zaidi et al. 2015) which was not included by the EAC. The review reported that 84% of patients receiving treatment with iFuse have a good response to treatment. However, this figure is a mean of patient satisfaction and this is used as a proxy for "good response to treatment". One of the EAC's included studies (Duhon et al. 2016) reported a composite success rate for surgery which the EAC felt was more applicable than the figure used by the company from Zaidi et al. (2015). The review also reported that on average 54% of patients receiving open surgery had a "good response to treatment" and states that this is based on patient satisfaction. However, the EAC checked a table in the review, which summarised the studies used to obtain a value of 54%, and noted the table contained other outcomes such as ODI, VAS and SF-36 results. The EAC did not feel it was correct to refer to an average of values obtained through different methodologies as "patient satisfaction". Therefore, the EAC obtained a value for "good response to treatment" from a study by Kibsgard et al. (2013), which was included in the review by Zaidi et al. (2015). Both of the values used by the EAC were 12 months post-treatment. The model uses the "good response to treatment" state as a pain-free state that does incur any costs.

The model submitted by the company also contained a variable for procedure time and was obtained from one study (Nystrom et al. 2017). However, the patients in this study were all women and another study by Ledonio et al. (2014a) also reports this outcome. The EAC therefore calculated a weighted average procedure time using both of these studies.

Resource identification, measurement and valuation

The company identified HRG codes for iFuse as HN13A-F Major hip procedures and codes for open surgery as HC53, 54, 60, 61,62,63,64 Spinal procedures. However in Tables C6 and C7 of the company submission these are reversed, so that the hip codes are assigned to open procedures. The

cost of a bed day is therefore incorrect for iFuse and open surgery. The incorrect values were used in the model.

In Table 9 of the company submission the HRG codes for RF ablation therapy are correctly identified, but the activity and reference costs for each code are described as outpatient, whereas these are the values for day case. It is unclear whether the company intended to use the day case or outpatient setting for RF ablation; however these are correctly described as day case costs elsewhere. Therefore the EAC has left these unchanged as this would not have made a difference to the model.

The procedure cost of steroid injections is a key driver in the model comparing iFuse with the stepped pathway. The company has identified 2 HRG codes for this procedure. The first is HC29B day-case inflammatory spinal conditions at £500 per case and the EAC agrees with this selection. The second is HN16A minimal hip procedures at £724 per case. The company calculated a weighted mean of these 2 costs and because there are a large number of hip procedures reported in the NHS reference data, the result is £637 per case. The EAC considers that the HC29B should be used alone, reducing the procedure cost to £500.

The EAC checked the drug costs for the low cost and high cost regimens used in the model and found lower costs for some of the drugs. The lower drug costs were used by the EAC to update the model.

Technology and comparators' costs

The costs used by the company in the open surgery pathway for iFuse are consistent with the list price provided by the manufacturer and a clinical expert stated that the consumables used with iFuse seem correct. Costs for the open procedure are not as clear. The EAC sought expert opinion on the consumables used for open surgery. One clinical expert noted that cannulated screws would be used for open surgery but could not comment on the exact consumables required without a full description of the open technique used; this was not described in detail by the company. Feedback from another clinical expert stated that open surgery would not be carried out very often

anymore. However, if it was to be carried out he believes that the posterior SIJ fixation would be the most costly procedure and this is in agreement with the company's submission.

The company's submitted model contains a stepped pathway and open surgery pathway. In the stepped pathway patients receive a steroid injection, recurrent steroid injections or radiofrequency ablation in a stepped manner.

Sensitivity analysis

The company carried out a deterministic sensitivity analysis. The ranges used for sensitivity analysis were set differently for each variable. Some used 95% CI from published data, others used nominal ranges, or a standard 20% in either direction. Where there is a lot of uncertainty, it is reasonable to have a wider range for sensitivity analysis. A variable that results in a large change in outcome may do so because of the large uncertainty (relative to the range used for other variables), rather than because of the importance of the variable in the model. Total pain management costs vary between £94.25 and £855.19 (almost 90% in either direction), contributing to its appearance as a key model driver. By contrast, iFUSE success rates vary between 79.8% and 88.2% (only 5% in either direction), which understats the importance of this input to the model, and does not reflect the uncertainty for this variable.

The company's deterministic sensitivity analysis identified some of the key drivers of the model as:

- probability of revision for open surgery
- total pain management
- % receiving anterior or posterior surgery
- unit cost of theatre time
- length of stay for open surgery
- consumables used

Compared to stepped pathway

- total pain management
- number of steroid injections in 6 months
- steroid procedure costs
- transition probabilities from steroid injections to other states

The EAC has investigated the cost of pain management and length of stay for open and iFuse surgery. The consumables used for open surgery are identified from published papers and in the interviews with clinical experts. However the costs of the consumables are more difficult to find with confidence. For example, NHS supply chain lists many different versions of the consumable items having a wide price range. In the deterministic sensitivity analysis the company looked at total consumables cost for posterior open surgery between £2,640 and £3,960 which is 20% either side of the base case value. The impact on the model result was that iFuse remained cost saving at between £3,882 and £4,664 per patient compared with open surgery.

Unit cost of theatre time is a key driver of the model, but probably presents limited opportunity to make a system impact. A few minutes saved in the operating theatre per patient is welcome, but if each surgeon does 90 operations in 5 years, the saved time has the potential to release 2 half day sessions per year for each surgeon.

A summary of the EAC's changes to parameters of the company's submitted model has been presented in Table 11. The table contains the values used by the company in their model, the source and some EAC comments in addition to the EAC's value, source and comments on why the value was chosen.

Table 11| EAC changes to parameters in the company's model.

Variable	Company value	Company source and EAC comments	EAC value	EAC source and comments
Length of stay for open surgery (anterior)	8 days	Nystrom et al. (2017) This study's participants were all women and another study by Ledonio et al. (2014a) also reports on length of stay for open surgery (anterior).	6.7 days	The EAC calculated a weighted average length of stay from the papers by Nystrom et al. (2017) and Ledonio et al. (2014a).
Length of stay for open surgery (posterior)	5.1 days	Smith et al. (2013). The company used the length of stay reported by Smith et al. (2013). This study was not included by the EAC as the study reported on outcomes of iFuse patients presented elsewhere.	4 days	The EAC consulted a table of included studies in the paper by Smith et al. (2013) and found that 4/9 of the included studies on posterior open surgery reported length of stay. The EAC calculated an average length of stay from the 4 studies (Khurana et al. 2009, Al-Khayer et al. 2008, Wise et al. 2008 and Buchowski et al. 2005) and this was different from the one presented by Smith et al. (2013). Therefore, the EAC calculated a weighted length of stay and used this.
Length of stay for iFuse	1.7	Heiney et al. (2015). The company used the length of stay presented by Heiney et al. (2015). This study was not included by the EAC in its	0.8	The EAC calculated a weighted average length of stay from its included studies reporting mean length of stay (Polly et al. 2016a, Duhon et al. 2016, Schroeder et al. 2013, Capobianco and Cher 2015).

Variable	Company value	Company source and EAC comments	EAC value	EAC source and comments
		included studies as the review was deemed to be of poor quality with high heterogeneity in its included studies.		
Procedure time for open surgery (anterior)	104 minutes	Nystrom et al. (2017) The company used the mean procedure time presented by Nystrom et al. (2017).	110.9 minutes	The EAC calculated a weighted mean procedure time from Nystrom et al. (2017) and Ledonio et al. (2014a).
HRG codes used for open surgery and iFuse (cost of bed day)	Open surgery: £380.99 iFuse: £272.32	NHS reference costs for 2015/2016. The company identified HN13A-F HRG codes (Major hip procedures) for iFuse and HC53, 54, 60, 61,62,63,64 HRG codes (Spinal procedures) for open surgery. However, the company has reversed these costs in its model and the costs for a bed day for iFuse and open surgery are therefore incorrect.	Open surgery: £272.32 iFuse: £380.99	NHS reference costs for 2015/2016. The EAC changed the cost of a bed day for open surgery and iFuse to what was originally stated in the company's submission.
Cost of steroid injections	£637	NHS reference costs for 2015/2016. The company calculated a weighted average from two HRG codes for steroid	£500	NHS reference costs for 2015/2016. The EAC used the HC29B HRG code only.

Variable	Company value	Company source and EAC comments	EAC value	EAC source and comments
		injections: HC29B (day-case inflammatory spinal conditions) at £500 per case and HN16A (minimal hip procedures) at £724 per case		
Low cost drug regimen	£63.25	December 2017 BNF/drug tariff The company calculated a price for a low cost drug regimen: Daily Regimen = co-codamol 4 x 8/500 mg + naproxen 2 x 500 mg + Omeprazole 20 mg	£27.38	December 2017 BNF/drug tariff The EAC found lower costs for the drugs listed by the company: • Co-codamol 4 x 8/500 mg = £0.04 • Naproxen 2 x 500 mg = £0.08 • Omeprazole 20 mg = £0.03 • £0.15 x 182.5 (6 monthly) = £27.38
High cost drug regimen	£692.98	The company calculated a price for a high cost drug regimen: Daily Regimen = tapentadol 2 x 200 mg + naproxen 2 x 500 mg + Omeprazole 20 mg	£669.78	December 2017 BNF/drug tariff The EAC found lower costs for the drugs listed by the company: • Tapentadol 2 x 200 mg = £3.56

Variable	Company value	Company source and EAC comments	EAC value	EAC source and comments
				• Naproxen 2 x 500 mg = £0.08 • Omeprazole 20 mg = £0.03 • £3.67 x 182.5 (6 monthly) = £669.78
Good response to treatment (%): iFuse	84%	Review by Zaidi et al. (2015). This review reported patient satisfaction.	79.9%	The EAC obtained a figure for success rate from a study by Duhon et al. (2016) at 12 months post-procedure. The success rate in this study was a composite endpoint where the procedure was deemed successful if there was: a reduction from baseline VAS SI joint pain by at least 20 points, absence of device-related serious adverse events, absence of neurological worsening related to the sacral spine, and absence of surgical re-intervention (removal, revision, reoperation, or supplemental fixation) for SI joint pain.
Good response to treatment (%): open surgery	54%	Review by Zaidi et al. (2015). The review presented patient satisfaction obtained using multiple methods.	48%	The EAC obtained a figure for success rate from a study by Kibsgard et al. (2013). This study was included in the review by Zaidi et al. (2015). The figure of 54% that Zaidi and colleagues reached was a mean across several studies. Not all of the studies presented results for patient satisfaction and so Zaidi and

Variable	Company value	Company source and EAC comments	EAC value	EAC source and comments
				colleagues pooled results for ODI, VAS, SF-36 and other measures. The EAC did not feel this was appropriate.
Procedure time: open, posterior	104 minutes	Nystrom et al. (2017). This study's participants were all women and another study by Ledonio et al. (2014a) also reports on procedure time for open surgery (anterior).	110.9 minutes	The EAC calculated a weighted average procedure time from the papers by Nystrom et al. (2017) and Ledonio et al. (2014a).

3.3 Interpretation of economic evidence

The company identified a total 5 previously published studies for their economic submission. Three of the studies were from a US payer perspective (Ackerman et al. 2014, Ackerman et al. 2014 and Cher at al. 2016), one study presented results on worker productivity (Saavoss et al. 2016) and one study presented results of a work-up for SIJ pain (Polly et al. 2016). In the 3 studies which present a cost analysis (Ackerman et al. 2014, Ackerman et al. 2014 and Cher at al. 2016), iFuse is compared to non-surgical care.

The company's base-case showed a cost saving of £4,273 per patient for iFuse compared to open surgery None of the studies included by the company compare iFuse to open surgery and therefore no comparisons can be made.

The company's base-case showed a cost saving of £325 per patient for iFuse compared to a stepped pathway. The company states that the results from their economic analysis are consistent with the academic literature. However, the focus of the papers by Ackerman et al. (2013) and Ackerman et al. (2014) are not specific to a UK perspective, and even choices such as the time horizon are determined by conventions for presenting economic models from these perspectives. Cher et al. (2016) finds iFuse to be more costly than non-operative care, taken from a US third party payer perspective over a 5 year time period. In this model iFuse becomes cost saving at a time horizon of 13 years. This model does not include the cost of pain management medication in either arm, it also assumes that the cost of providing non-operative care reduces by 50% after the first 6 months of treatment. Both of these assumptions are likely to favour the non-operative treatment. Ackerman et al. (2013) is described as a lifetime perspective, but appears to be a 15 year time horizon with no mortality rate modelling described. This model finds a saving of $3,358 per patient for iFuse over the time horizon modelled. This model does include pharmaceutical costs, however they are measured as increasing over the initial 3 years, and then extrapolated linearly for the remaining time. This is likely to overestimate the cost of the non-operative treatment. Ackerman et al. (2014) takes a 3 year time horizon, and finds iFuse to be

more costly by $14,545 at 3 years. The two arms are cost neutral at 6 years and this is more consistent with the company's base-case results at 7 years.

3.4 Results of EAC analysis

The EAC identified two errors in the model which were addressed before other changes to the model were made (Appendix D – EAC changes to errors in the company's submitted model). One error affected the cost of the stepped pathway. The EAC used the latter approach and this lead to iFuse becoming more cost saving, as more people continue to use steroid injections, which are the most costly option in the stepped pathway (Table 12).

Table 12| Results of EAC's change to 6-monthly probability of discontinuation of steroid treatment on the cost of the stepped pathway

	iFuse cost per patient	**Stepped pathway cost per patient**	**Difference in cost per patient between treatment pathways**
Before change was made by EAC	£7,318.99	£7,644.06	-£325.07
After change was made by EAC	£7,318.99	£7,824.24	-£505.25
Difference in treatment cost per patient following EAC change.	£0.00	£180.18	

The second error in the model identified by the EAC related to the calculations of late revision and affected the cost of the open surgery. The EAC's change makes open surgery slightly more effective, and less costly. However, the impact is very low due to the small number of revisions (Table 13).

Table 13| Results of EAC's change to the revision probability on the cost of open surgery

	iFuse cost per patient	**Open surgery cost per patient**	**Difference in cost per patient between treatment pathways**
Before change was made by EAC	£7,318.99	£11,591.85	-£4,272.86
After change was made by EAC	£7,318.99	£11,499.62	-£4,180.63
Difference in treatment cost per patient following EAC change.	£0.00	-£92.23	

Base-case analysis results

The EAC made changes to parameters in the company's model as previously described (Table 11) after addressing the two identified errors as described in Table 12 and Table 13. The EAC's base-case results are presented in Table 14.

Table 14| EAC's base-case

	iFuse	**Open surgery**	**Stepped pathway**
Theatre & Hospital Costs	£1,309.56	£3,789.17	-
Consumable Cost	£4,059.00	£2,260.00	-
Follow-up	£570.90	£570.90	-
Early Revision	£25.65	£106.72	-
Training Cost	£6.09	-	-
Medication	£1,060.95	£2,627.21	£3,640.82

Late Revision	£269.72	£1,111.34	-
Steroid Injections	-	-	£3,043.23
RF Ablations	-	-	£60.60
Total	**£7,301.87**	**£10,465.34**	**£6,744.65**
Incremental	**-**	**-£3,163.46**	**+£557.22**

Sensitivity analysis results

The EAC carried out a one-way sensitivity analysis after making changes to the company's model.

For iFuse vs. open surgery, the main driver for cost saving was the bi-annual probability of revision (Figure 4). Other important factors included length of stay for iFuse, % anterior/posterior open surgery procedures, total pain management, unit cost of theatre time and total consumables for iFuse. A wider sensitivity range for the success rate of iFUSE would result in this also being an important factor. Values for the inputs and results of the one way sensitivity analysis have been presented in Appendix D – EAC changes to errors in the company's submitted model and Appendix E – Values for inputs and results from EAC's one way sensitivity analysis It is worth noting that none of the variables in the model made iFuse cost incurring against open surgery in the one-way sensitivity analysis.

For iFuse vs. the stepped pathway, the main drivers for incurring cost were total pain management and the number of steroid injection procedures in 6 months (Figure 5). Other important factors included length of stay for iFuse, % good response to steroid injection treatment, unit cost of theatre time and steroid injection procedure costs. A wider sensitivity range for the response to iFUSE would result in this also being an important factor. Values for the inputs and results of the one way sensitivity analysis have been presented in Appendix E – Values for inputs and results from EAC's one way sensitivity analysis The sensitivity analysis highlights that a number of variables can increase the cost savings associated with iFuse and conversely can make iFuse cost incurring. The analysis shows that the pain management followed by patients receiving treatment with iFuse or in the stepped pathway can lead

to a cost saving for iFuse and can cause iFuse to become cost incurring. This is reflective of the variable nature of pain management for an individual. In addition, the number of steroid injections received during 6 months is a driver of the model. If a patient was to have a higher number of steroid injections during 6 months then iFuse would become cost saving. The EAC sought expert advice and patients would typically receive a steroid injection every 6 months as modelled by the company in their submission. Our analysis shows that length of stay can also lead to cost savings for iFuse. The lowest length of stay for iFuse in the literature was 0 days (Duhon et al. 2016) and this was used as a lower limit in the one-way sensitivity analysis. However, a length of stay will not realistically be 0. In all likelihood this was used by the authors of the study to show that a patient was discharged on the same day as their procedure.

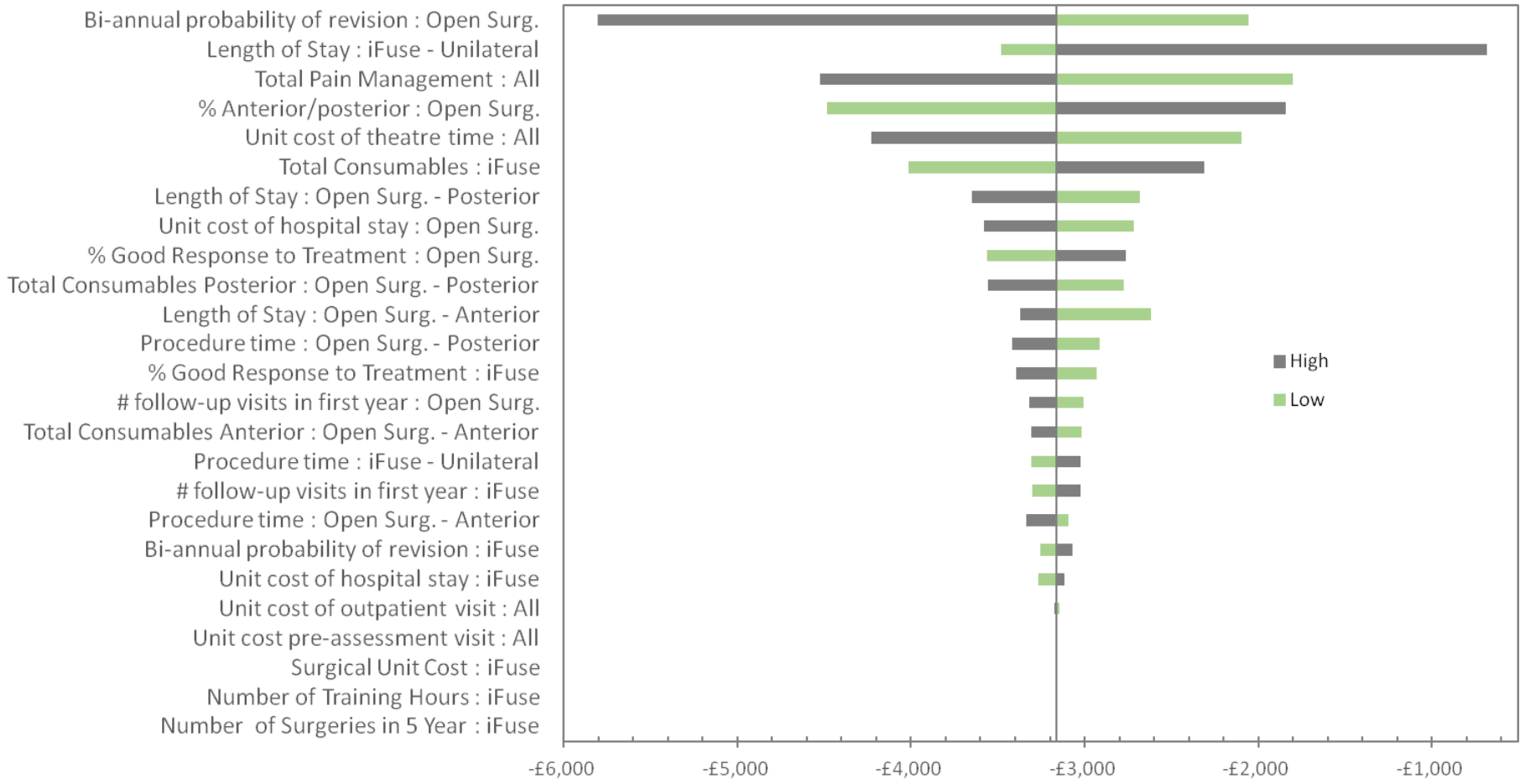

Figure 4| Tornado diagram of EAC's one way sensitivity analysis, showing the parameters with the highest impact for iFuse vs. open surgery. The ranges used by the EAC have been presented in Appendix E – Values for inputs and results from EAC's one way sensitivity analysis

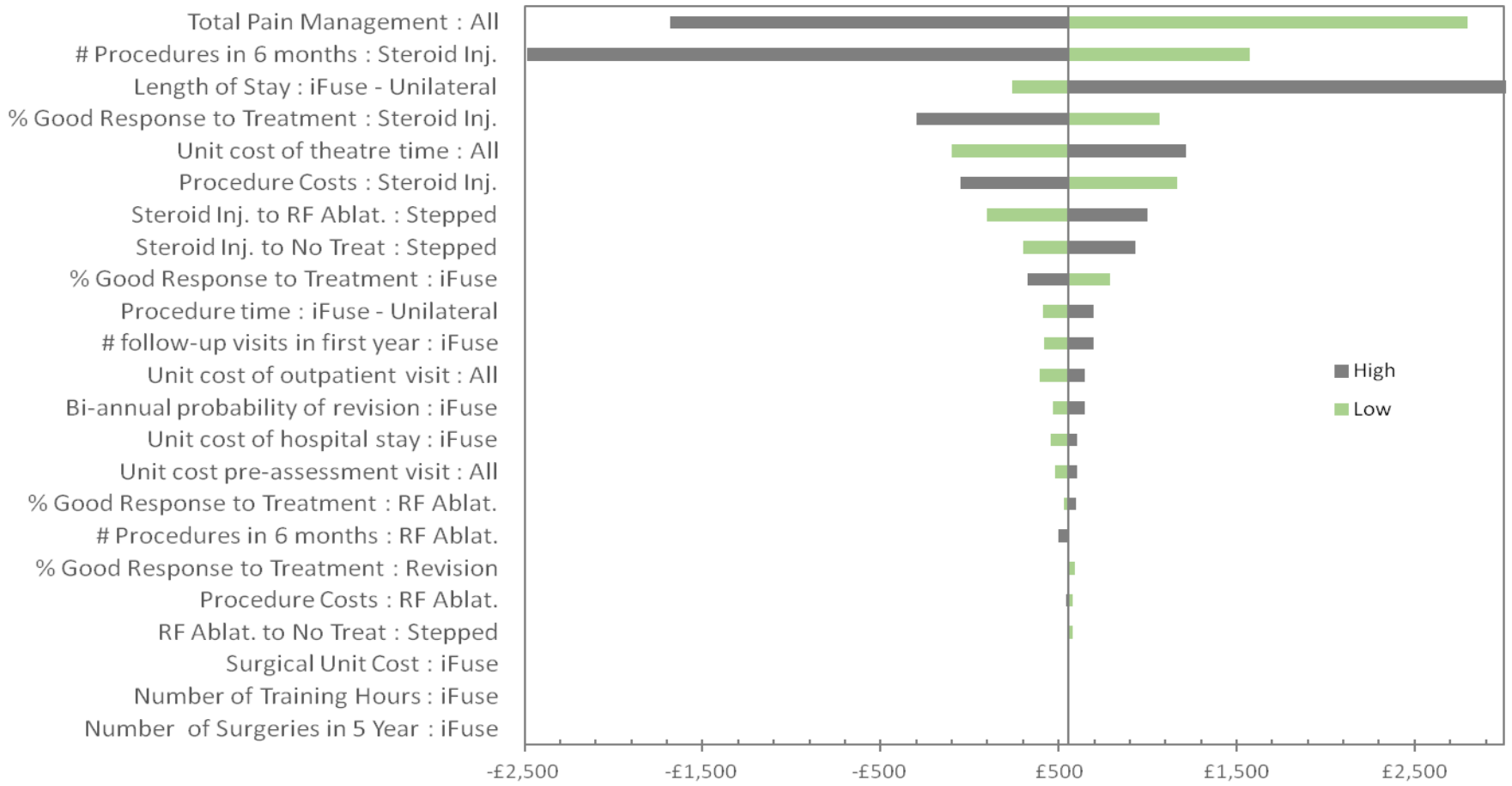

Figure 5| Tornado diagram of EAC's one way sensitivity analysis, showing the parameters with the highest impact for iFuse vs. the stepped pathway. The ranges used by the EAC have been presented in Appendix E – Values for inputs and results from EAC's one way sensitivity analysis

Subgroup analysis

The EAC did not carry out subgroup analysis.

Model validation

The company details internal validation of the model and external validation with clinical experts. The additional economic papers are also used as a form of external validation for the stepped pathway comparator. Of the three relevant papers (Ackerman 2013, Ackerman 2014 and Cher 2016) only one finds iFuse cost saving at the base case time horizon chosen by the authors, however all do have a point at which iFuse becomes cost saving.

Some differences which were noted are that the overall cost of providing iFuse or a stepped pathway are higher in the US based model, and that all the models include provision for post-operative physiotherapy in the iFuse pathway. Cher (2016) did not include pain medication costs which is likely favour the comparator substantially. The stepped pathway costs were taken from overall treatment costs for a group of patients, rather than individual costs for each treatment.

There are large differences between these papers and a UK model in terms of relevant perspective and appropriate costs and sources of information. There are also issues with modelling assumptions. Despite these reservations, the published models do support the finding that iFuse will become cost saving over a sufficient time horizon compared to stepped treatment.

3.5 EAC Interpretation of economic evidence

The company's submitted model contained two different comparator pathways. The structure of the model for iFuse vs. open surgery was simpler than the company's model for iFuse vs. a stepped pathway. Changes made to the company's submitted model have previously been presented (seeTable 11). A full list of the parameters influencing the model and the values used as part of the EAC's sensitivity analysis has been presented in (Appendix E – Values for inputs and results from EAC's one way sensitivity analysis, Appendix D – EAC changes to errors in the company's submitted model) Results following the EAC's changes to the model have previously been

presented (see Results of EAC analysis). The impact of the EAC's changes to the company's model have been summarised below (see Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre section).

The company's submission contained many assumptions and these have been previously discussed (Table 9). The company's base case showed iFuse to be cost saving when used instead of open surgery or in place of a stepped pathway. The EAC used evidence from published studies whenever available in an effort to base model results on meaningful clinical data. The EAC also addressed what it believes were two errors in the model and also ensured that inputs stated in the company's economic submission were used correctly in the model. The EAC also made changes to costs based on HRG codes where appropriate. The changes to the model by the EAC reduced the cost savings presented for iFuse in its base-case when used in place of open surgery at a time horizon of 7 years. Following changes to the model by the EAC, iFuse was shown to be cost-incurring compared to a stepped pathway at a time horizon of 7 years but would become cost-saving if the horizon was extended to 9 years.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

After the two errors in the company's model EAC were addressed by the EAC, the company's base-case showed a cost saving of £4,272.86 per patient compared to open surgery and a cost saving of £325.07 per patient compared to a stepped pathway over a 7 year time horizon. The EAC made further changes to the company's model. The EAC's base-case analysis shows that the use of iFuse would save £3,093.90 per patient compared to the use of open surgery and would incur a cost of £557.22 compared to the use of a stepped pathway over a 7 year time horizon. The effect of the additional changes to parameters by the EAC, which have driven the difference in cost savings between the EAC's and company's base-case have been presented in Table 15. The table presents the impact of changes individually and not cumulatively.

Table 15| Changes to the company's model by the EAC and its effect on cost savings (the effect of each individual change on the model has been presented and is not cumulative).

EAC changes to company's model	**Company's base case.** **Cost per patient**	**Company's base case.** **Cost saving per patient**	**EAC model changes.** **Cost per patient**	**EAC model changes.** **Cost saving per patient**
iFuse vs. open surgery				
The EAC changed the length of stay for open surgery (anterior) from 8 to 6.7 days.	iFuse: £7,318.99 Open surgery: £11,499.62	-£4,180.63	iFuse: £7,318.99 (no change) Open surgery: £11,206.41	-£3,887.42
The EAC changed the length of stay for open surgery (posterior) from 5.1 to 4 days.	As above.	As above.	iFuse: £7,318.99 (no change) Open surgery: £11,251.52	-£3,932.53
The EAC changed the length of stay for iFuse from 1.7 to 0.8 days.	As above.	As above.	iFuse: £7,061.71 Open surgery: £11,499.62 (no change)	-£4,437.91
The EAC changed the procedure time for open surgery (anterior) from 104 to 110.9 minutes.	As above.	As above.	iFuse: £7,318.99 (no change) Open surgery: £11,569.18	-£4, 250.19

The EAC changed the HRG codes used for the cost of iFuse and open surgery. The company reversed the costs for the two procedures in their model so the EAC swapped the cost codes back to match the ones listed in the company's submission: Changed the unit cost of hospital stay for iFuse from £272.32 to £380.99 and changed the unit cost of hospital stay for open surgery from £380.99 to £272.32.	As above.	As above.	iFuse: £7,512.91 Open surgery: £10,656.87	-£3,143.95
iFuse vs. stepped pathway				
The EAC changed the HRG codes used for the cost of steroid injections from £637.69 to £500.	iFuse: £7,318.99 Stepped pathway: £7,824.24	-£505.25	iFuse: £7,318.99 (no change) Stepped pathway: £6,986.20	+£332.79 (iFuse is cost incurring)
iFuse vs. stepped pathway or open surgery				

The EAC changed the cost of a low drug regimen cost from £63.25 to £27.38 and high drug regimen cost from £692.98 to £669.78.	iFuse: £7,318.99 Open surgery: £11,499.62 Stepped pathway: £7,824.24	iFuse vs. open surgery: -£4,180.63 iFuse vs. stepped pathway: -£505.25	iFuse: £7,262.25 Open surgery: £11,349.99 Stepped pathway: £7,582.70	iFuse vs. open surgery: -£4,081.75 iFuse vs. stepped pathway: -£320.45
The EAC changed the good response to treatment (iFuse) from 84% to 79.9%.	As above.	As above.	iFuse: £7,538.28 Open surgery: £11,499.62 (no change) Stepped pathway: £7,824.24 (no change)	iFuse vs. open surgery: -£3,961.34 iFuse vs. stepped pathway: -£285.97
The EAC changed the good response to treatment (open surgery) from 54% to 48%.	As above.	As above.	iFuse: £7,318.99 (no change) Open surgery: £11,799.74 Stepped pathway: £7,824.24 (no change)	iFuse vs. open surgery: -£4,480.75 iFuse vs. stepped pathway: -£505.25

The EAC's results for iFuse vs. the stepped pathway show that iFuse was cost incurring over a 7 year time horizon. Therefore, the EAC undertook extra analysis in order to determine when iFuse would become cost saving against the stepped pathway. In year 9 iFuse would save £494.57 per patient.

4 Conclusions

4.1 Conclusions on the clinical evidence

A total of 12 studies were included by the EAC. The EAC also identified one case report (Palmiere et al. 2017) which was discussed in section 2.7 (adverse events). Two RCTs compared the use of iFuse against CM/NSM (Dengler et al. 2017b and Polly et al. 2016). Both RCTs showed a significant improvement in pain, ODI and EQ-5D following SIJF with iFuse. Furthermore, both RCTs showed that the observed improvements in pain, ODI and EQ-5D were significantly higher for patients treated with iFuse than those receiving CM/NSM. In addition, one RCT (Polly et al. 2016) showed that patient satisfaction was significantly higher in patients receiving iFuse than those receiving NSM. One comparative study (Vanaclocha et al. 2018) showed a significant improvement in pain and ODI for patients treated with iFuse and the improvement was significantly higher than improvements observed from CM and SID using RF ablation. There were a total of 7 non-comparative studies. These studies showed that iFuse significantly improved pain scores (5/5 studies reporting this outcome), ODI (5/5 studies reporting this outcome) and HRQoL (3/3 studies reporting this outcome). A total of 8/12 studies reported the number of device/treatment related events, 10/12 studies reported the number of postoperative infection or complications and 10/12 studies reported the number of reoperation/revision rates. One comparative study (Spain and Holt 2017) showed that the reoperation/revision rate was lower for iFuse than that for open SIJ fixation using screws. Sub-group analysis (Capobianco and Cher 2015) showed a significant improvement in pain, ODI and HRQoL following SIJF with iFuse in women with PPGP, women with no PPGP and men with no significant difference across the three groups. The EAC found no evidence for time to return to work/normal activities.

The evidence identified by the EAC presents an unbiased estimate of the technology's treatment effect and is relevant to the scope as the population, intervention, comparators and outcomes match the scope. The EAC has included two RCTs and two comparative studies. However, the majority of the evidence is non-comparative and of the comparative evidence only one study

compares iFuse to open SIJ fusion and this study presents revision rates only. The evidence submitted by the company contained a number of studies where there was patient overlap and these were excluded by the EAC. Of the 12 studies included by the EAC, 9 were sponsored by the company and at least one study author was an employee of the company.

4.2 Conclusions on the economic evidence

The company's economic submission effectively contained two economic models, one for iFuse vs. open surgery and another for iFuse vs. a stepped pathway. The EAC made changes to each model where appropriate and as such obtained different results to those presented in the company's base-case. The EAC's changes decreased the cost savings for iFuse vs. open surgery presented by the company in its base-case. However, the EAC's results still showed iFuse to be cost saving when used in place of open surgery. Furthermore, iFuse remained cost saving throughout the EAC's one-way sensitivity analysis as the procedure is less costly and leads to better outcomes than open surgery.

The EAC's changes lead to iFuse becoming cost incurring when used in place of a stepped pathway whilst the company's results showed iFuse to be cost saving. The company's model used a 7 year time horizon. Following further analysis the EAC determined that iFuse would become cost saving against a stepped pathway at 9 years. The EAC's one-way sensitivity analysis highlighted the uncertainty in terms of cost for the use of iFuse vs. a stepped pathway. Upfront costs for iFuse are high but may result in relatively low annual costs whilst the stepped pathway has a moderate annual cost that remains relatively constant over time. The EAC showed that iFuse becomes cost saving over the stepped pathway if a longer time horizon is used. Any further changes in the inputs are likely to result in iFuse remaining cost saving compared to the stepped pathway given a sufficiently long time horizon.

The company's submitted economic evidence did not reflect the decision problem as outcomes were not appropriate, were from a perspective outside of scope or were not based on the UK clinical pathway. However, the

submitted economic model matched the decision problem defined in the scope.

5 Summary of the combined clinical and economic sections

The EAC included a total of 12 studies and discussed the results of an additional case report presenting results on an adverse event. The clinical evidence shows that SIJF using iFuse significantly improved patient pain, ODI and health-related quality of life when compared to conservative/non-surgical management, in non-comparative studies and in women with post-partum pelvic girdle pain. In addition, iFuse was shown to require fewer revisions than open surgery using screws. Some adverse events were associated with the procedure for SIJF using iFuse. The EAC identified patient overlap between studies, and therefore excluded studies where patient outcomes had been presented elsewhere. The EAC's changes to the company's submitted model showed iFuse to be cost saving when used in place of open surgery and cost incurring when used in place of a stepped pathway over a 7 year time horizon. However, iFuse was shown to be cost saving against a stepped pathway at a longer time horizon.

6 Implications for research

The EAC identified a lack of evidence comparing the use of iFuse to open surgery. However, further research into this area may not be appropriate as open surgery may not be the most appropriate treatment now that a minimally invasive option is available. Some evidence on this was listed as relevant by the company (Ledonio et al. 2014a, Ledonio et al. 2014b) but was not included by the EAC due to the patients included in these studies being presented elsewhere.

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Appendices

Appendix A – Company and EAC literature search strategies and PRISMA diagrams.

Appendix B – Patient origin for company submitted studies.

Appendix C – EAC critical appraisal of included studies.

Appendix D – EAC changes to errors in the company's submitted model

Appendix E – Values for inputs and results from EAC's one way sensitivity analysis.

Appendix A - Company and EAC literature search strategies and PRISMA diagrams

Company search strategy

The company identified relevant studies through its own monitoring. However, no details were given on how this monitoring was carried out. The company also carried out a simplistic search in Medline using the search terms "sacroiliac joint AND (fusion OR arthrodesis)". The company did not identify any other additional studies using this search.

The company did not present a PRISMA diagram of their submitted studies.

EAC search strategy

The EAC used the reference list from a NICE interventional procedures overview (IPO) for IPG578 (Minimally invasive sacroiliac joint fusion surgery for chronic sacroiliac pain) to obtain relevant clinical evidence studies for this assessment. Literature searching for the IPO was carried out in January 2017. The EAC therefore carried out an updated search to capture any studies published after January 2017. For economic evidence the EAC conducted searches from 2008 onwards. iFuse was obtained CE mark status in 2010 therefore using a filter 0f 2008 onwards would allow any preliminary work to be captured.

Clinical evidence search strategy

Ovid MEDLINE(R)

1 Minimally Invasive Surgical Procedures/ (23312)

2 Spinal Fusion/ (22384)

3 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (fusion or fuse* or arthrodes* or surg* or immobili* or fixat*)).tw. (1047)

4 (MIS adj4 fus*).tw. (201)

5 (minimal* adj4 invas* adj4 fus*).tw. (670)

6 (spin* adj4 (hardware or fus* or fixat*)).tw. (11524)

7 Titanium/ and "Prostheses and Implants"/ (6758)

8 (titanium adj4 implant*).tw. (2551)

9 BMP.tw. (16714)

10 'bone morphogenetic protein*'.tw. (16117)

11 (ifuse or i-fuse).tw. (19)

12 SImmetry.tw. (6)

13 SI-BONE.tw. (8)

14 or/1-13 (80928)

15 Sacroiliac Joint/ (3910)

16 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (dysfunct* or disrupt* or pain* or degenerat* or inflamm* or injur* or hypermobil* or syndrome* or fracture*)).tw. (2302)

17 sacroiliitis.tw. (1873)

18 Pelvic Bone/ (9151)

19 (pelvic adj4 (bone* or ring*)).tw. (3625)

20 or/15-19 (16955)

21 14 and 20 (735)

22 Animals/ (6517628)

23 Humans/ (17846574)

24 22 not (22 and 23) (4649407)

25 21 not 24 (716)

26 limit 25 to yr=”2017-Current” (50)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

1 Minimally Invasive Surgical Procedures/ (8)

2 Spinal Fusion/ (0)

3 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (fusion or fuse* or arthrodes* or surg* or immobili* or fixat*)).tw. (201)

4 (MIS adj4 fus*).tw. (57)

5 (minimal* adj4 invas* adj4 fus*).tw. (171)

6 (spin* adj4 (hardware or fus* or fixat*)).tw. (1364)

7 Titanium/ and "Prostheses and Implants"/ (0)

8 (titanium adj4 implant*).tw. (703)

9 BNP.tw. (742)

10 'bone morphogenetic protein*'.tw. (1151)

11 (ifuse or i-fuse).tw. (10)

12 SImmetry.tw. (1)

13 SI-BONE.tw. (3)

14 or/1-13 (4151)

15 Sacroiliac Joint/ (0)

16 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (dysfunct* or disrupt* or pain* or degenerat* or inflamm* or injur* or hypermobil* or syndrome* or fracture*)).tw. (346)

17 sacroiliitis.tw. (160)

18 Pelvic Bone/ (0)

19 (pelvic adj4 (bone* or ring*)).tw. (335)

20 or/15-19 (785)

21 14 and 20 (91)

22 Animals/ (5536)

23 Humans/ (7723)

24 22 not (22 and 23) (225)

25 21 not 24 (91)

26 limit 25 to yr=”2017-Current” (24)

EMBASE

1 minimally invasive surgery/ (33862)

2 Spine Fusion/ (21413)

3 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (fusion or fuse* or arthrodes* or surg* or immobili* or fixat*)).tw. (1455)

4 (MIS adj4 fus*).tw. (279)

5 (minimal* adj4 invas* adj4 fus*).tw. (869)

6 (spin* adj4 (hardware or fus* or fixat*)).tw. (14857)

7 Titanium/ and "Prostheses and Orthoses"/ (628)

8 (titanium adj4 implant*).tw. (6933)

9 BMP.tw. (21294)

10 'bone morphogenetic protein*'.tw. (18645)

11 (ifuse or i-fuse).tw. (25)

12 SImmetry.tw. (22)

13 SI-BONE.tw. (18)

14 or/1-13 (96907)

15 Sacroiliac Joint/ (6254)

16 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (dysfunct* or disrupt* or pain* or degenerat* or inflamm* or injur* or hypermobil* or syndrome* or fracture*)).tw. (3229)

17 sacroiliitis.tw. (2837)

18 Pelvic Girdle/ (6183)

19 (pelvic adj4 (bone* or ring*)).tw. (4758)

20 or/15-19 (18705)

21 14 and 20 (815)

22 Animals/ (1668914)

23 Humans/ (13420376)

24 22 not (22 and 23) (1312542)

25 21 not 24 (807)

26 limit 25 to yr=”2017-Current” (59)

Scopus

(((ABS ("Spinal Fusion") AND PUBYEAR > 2016) OR (ABS ("Minimally Invasive Surgical Procedure*") AND PUBYEAR > 2016) OR (ABS (((sacrum OR sacroiliac OR sacro-iliac OR sij) W/4 (fusion OR fuse* OR arthrodes* OR surg* OR immobili* OR fixat*))) AND PUBYEAR > 2016) OR (ABS ((mis W/4 fus*)) AND PUBYEAR > 2016)) OR ((ABS ((minimal* W/4 invas* AND adj4 AND fus*)) AND PUBYEAR > 2016) OR (ABS (titanium AND prostheses) AND PUBYEAR > 2016) OR (ABS (titanium AND implants) AND PUBYEAR > 2016) OR (ABS ("bone morphogenetic protein") AND PUBYEAR > 2016) OR (ABS (ifuse OR Ifuse) AND PUBYEAR > 2016) OR (ABS

(simmetry OR sibone) AND PUBYEAR > 2016))) AND ((ABS (("SacroiliacJoint")) AND PUBYEAR > 2016) OR (ABS (((sacrum OR sacroiliac OR sacroiliac OR sij) W/3 (dysfunct* OR disrupt* OR pain* OR degenerat* OR inflamm* OR injur* OR hypermobil* OR syndrome* OR fracture*))) AND PUBYEAR > 2016) OR (ABS (sacroiliitis OR "pelvic bone" OR "pelvic ring") AND PUBYEAR > 2016))

Cochrane Library (all relevant components)

#1 MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only (1090)

#2 MeSH descriptor: [Spinal Fusion] this term only (1110)

#3 (sacrum or SI or sacroiliac or sacro-iliac or SIJ) next/4 (fusion or fuse* or arthrodes* or surg* or immobili* or fixat*):ti,ab,kw (Word variations have been searched) (626)

#4 Ifuse:ti,ab,kw (Word variations have been searched) (11)

#5 I-fuse:ti,ab,kw (Word variations have been searched) (0)

#6 #1 or #2 or #3 or #4 or #5 (2742)

#7 MeSH descriptor: [Titanium] this term only (791)

#8 #6 AND #7 (26)

#9 MeSH descriptor: [Sacroiliac Joint] this term only (107)

#10 #8 AND #9 (1)

Web of Science

#1 TS=("Minimally Invasive Surgical Procedure*") Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (98)

#2 TS=("Spinal Fusion")
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (463)

#3 **TOPIC:** ((sacrum or sacroiliac or sacro-iliac or SIJ) same (fusion or fuse* or arthrodes* or surg* or immobili* or fixat*))
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (171)

#4 TS=(Titanium and Prostheses)
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (243)

#5 **TOPIC:** (titanium and implant*)
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (1,730)

#6 **TOPIC:** ("bone morphogenetic protein*")
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (1,088)

#7 **TOPIC:** (ifuse or i-fuse)
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (4)

#8 **TOPIC:** (SImmetry)
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (2)

#9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (3,507)

#10 **TOPIC:** ("Sacroiliac Joint")
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (155)

#11 **TOPIC:** (((sacrum or sacroiliac or sacro-iliac or SIJ) SAME (dysfunct* or disrupt* or pain* or degenerat* or inflamm* or injur* or hypermobil* or syndrome* or fracture*)))
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (302)

#12 **TOPIC:** (sacroiliitis)
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (95)

#13 TS=("Pelvic Bone*")
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (66)

#14 TS=("Pelvic ring*")
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (80)

#15 #14 OR #13 OR #12 OR #11 OR #10
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (492)

#16 #15 AND #9
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (127)

#17 #15 AND #9
Refined by: [excluding] **WEB OF SCIENCE CATEGORIES:** (VETERINARY SCIENCES OR ZOOLOGY)
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=2017 (121)

Pubmed (published ahead of print)

'pubstatusaheadofprint' AND (ifuse) AND (sacroiliac) AND ("2017/01/01"[PDat] : "2017/12/31"[PDat]) (1)

MHRA

Ifuse AND (fusion OR SI-BONE)

IFUSE OR I-FUSE OR SI-BONE

ICTRP

Ifuse AND (fusion OR SI-BONE) (3)

Clinicaltrials.gov

Ifuse AND (fusion OR SI-BONE) (5)

Manufacturer's website

SPINAL FUSION AND (IFUSE OR I-FUSE) - limited by Date: 2016 – 2017 (1)

National Technical Reports Library

SPINAL FUSION AND (IFUSE OR I-FUSE) – limited by Date: 2016 – 2017

IFUSE OR I-FUSE OR SI-BONE - limited by Date: 2016 – 2017

SPINAL FUSION AND BONE - limited by Date: 2016 – 2017

Economic evidence search strategy

Ovid MEDLINE(R)

1 Minimally Invasive Surgical Procedures/ (23312)

2 Spinal Fusion/ (22384)

3 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (fusion or fuse* or arthrodes* or surg* or immobili* or fixat*)).tw. (1047)

4 (MIS adj4 fus*).tw. (201)

5 (minimal* adj4 invas* adj4 fus*).tw. (670)

6 (spin* adj4 (hardware or fus* or fixat*)).tw. (11524)

7 Titanium/ and "Prostheses and Implants"/ (6758)

8 (titanium adj4 implant*).tw. (2551)

9 BMP.tw. (16714)

10 'bone morphogenetic protein*'.tw. (16117)

11 (ifuse or i-fuse).tw. (19)

12 SImmetry.tw. (6)

13 SI-BONE.tw. (8)

14 or/1-13 (80928)

15 Sacroiliac Joint/ (3910)

16 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (dysfunct* or disrupt* or pain* or degenerat* or inflamm* or injur* or hypermobil* or syndrome* or fracture*)).tw. (2302)

17 sacroiliitis.tw. (1873)

18 Pelvic Bone/ (9151)

19 (pelvic adj4 (bone* or ring*)).tw. (3625)

20 or/15-19 (16955)

21 14 and 20 (735)

22 Economics/ (27494)

23 exp "costs and cost analysis"/ (224968)

24 Economics, Dental/ (1905)

25 exp economics, hospital/ (23588)

26 Economics, Medical/ (9205)

27 Economics, Nursing/ (4019)

28 Economics, Pharmaceutical/ (3003)

29 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (686564)

30 (expenditure$ not energy).ti,ab. (26297)

31 value for money.ti,ab. (1459)

32 budget$.ti,ab. (26372)

33 or/22-32 (833241)

34 ((energy or oxygen) adj cost).ti,ab. (3946)

35 (metabolic adj cost).ti,ab. (1289)

36 ((energy or oxygen) adj expenditure).ti,ab. (23543)

37 or/34-36 (27789)

38 33 not 37 (826803)

39 letter.pt. (1035368)

40 editorial.pt. (470380)

41 historical article.pt. (358181)

42 or/39-41 (1845674)

43 38 not 42 (792450)

44 exp animals/ not humans/ (4743207)

45 43 not 44 (743082)

46 bmj.jn. (75602)

47 "cochrane database of systematic reviews".jn. (14618)

48 health technology assessment winchester england.jn. (1294)

49 or/46-48 (91514)

50 45 not 49 (736954)

51 21 and 50 (17)

52 limit 51 to yr="2008 -Current" (14)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

1 Minimally Invasive Surgical Procedures/ (8)

2 Spinal Fusion/ (0)

3 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (fusion or fuse* or arthrodes* or surg* or immobili* or fixat*)).tw. (203)

4 (MIS adj4 fus*).tw. (60)

5 (minimal* adj4 invas* adj4 fus*).tw. (173)

6 (spin* adj4 (hardware or fus* or fixat*)).tw. (1417)

7 Titanium/ and "Prostheses and Implants"/ (0)

8 (titanium adj4 implant*).tw. (707)

9 BMP.tw. (1284)

10 'bone morphogenetic protein*'.tw. (1199)

11 (ifuse or i-fuse).tw. (10)

12 SImmetry.tw. (1)

13 SI-BONE.tw. (3)

14 or/1-13 (4156)

15 Sacroiliac Joint/ (0)

16 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (dysfunct* or disrupt* or pain* or degenerat* or inflamm* or injur* or hypermobil* or syndrome* or fracture*)).tw. (360)

17 sacroiliitis.tw. (156)

18 Pelvic Bone/ (0)

19 (pelvic adj4 (bone* or ring*)).tw. (345)

20 or/15-19 (807)

21 14 and 20 (94)

22 Economics/ (2)

23 exp "costs and cost analysis"/ (15)

24 Economics, Dental/ (1)

25 exp economics, hospital/ (0)

26 Economics, Medical/ (0)

27 Economics, Nursing/ (0)

28 Economics, Pharmaceutical/ (6)

29 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (92252)

30 (expenditure$ not energy).ti,ab. (2615)

31 value for money.ti,ab. (199)

32 budget$.ti,ab. (3720)

33 or/22-32 (95999)

34 ((energy or oxygen) adj cost).ti,ab. (475)

35 (metabolic adj cost).ti,ab. (150)

36 ((energy or oxygen) adj expenditure).ti,ab. (1995)

37 or/34-36 (2551)

38 33 not 37 (95244)

39 letter.pt. (44548)

40 editorial.pt. (41232)

41 historical article.pt. (39)

42 or/39-41 (85818)

43 38 not 42 (94315)

44 exp animals/ not humans/ (227)

45 43 not 44 (94315)

46 bmj.jn. (2273)

47 "cochrane database of systematic reviews".jn. (166)

48 health technology assessment winchester england.jn. (130)

49 or/46-48 (2569)

50 45 not 49 (94142)

51 21 and 50 (6)

52 limit 51 to yr="2008 -Current" (6)

EMBASE_ECON

1 minimally invasive surgery/ (34065)

2 Spine Fusion/ (21498)

3 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (fusion or fuse* or arthrodes* or surg* or immobili* or fixat*)).tw. (1463)

4 (MIS adj4 fus*).tw. (280)

5 (minimal* adj4 invas* adj4 fus*).tw. (872)

6 (spin* adj4 (hardware or fus* or fixat*)).tw. (14946)

7 Titanium/ and "Prostheses and Orthoses"/ (629)

8 (titanium adj4 implant*).tw. (6964)

9 BMP.tw. (21405)

10 'bone morphogenetic protein*'.tw. (18743)

11 (ifuse or i-fuse).tw. (25)

12 SImmetry.tw. (22)

13 SI-BONE.tw. (18)

14 or/1-13 (97438)

15 Sacroiliac Joint/ (6288)

16 ((sacrum or SI or sacroiliac or sacro-iliac or SIJ) adj4 (dysfunct* or disrupt* or pain* or degenerat* or inflamm* or injur* or hypermobil* or syndrome* or fracture*)).tw. (3254)

17 sacroiliitis.tw. (2869)

18 Pelvic Girdle/ (6222)

19 (pelvic adj4 (bone* or ring*)).tw. (4783)

20 or/15-19 (18834)

21 14 and 20 (823)

22 Health Economics/ (35671)

23 exp Economic Evaluation/ (270139)

24 exp Health Care Cost/ (259977)

25 pharmacoeconomics/ (6696)

26 22 or 23 or 24 or 25 (481694)

27 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (879141)

28 (expenditure$ not energy).ti,ab. (34189)

29 (value adj2 money).ti,ab. (2040)

30 budget$.ti,ab. (32934)

31 27 or 28 or 29 or 30 (910905)

32 26 or 31 (1122199)

33 letter.pt. (1001668)

34 editorial.pt. (554739)

35 note.pt. (698210)

36 33 or 34 or 35 (2254617)

37 32 not 36 (1031292)

38 (metabolic adj cost).ti,ab. (1312)

39 ((energy or oxygen) adj cost).ti,ab. (4038)

40 ((energy or oxygen) adj expenditure).ti,ab. (27973)

41 38 or 39 or 40 (32285)

42 37 not 41 (1024546)

43 animal/ (1820405)

44 exp animal experiment/ (2197178)

45 nonhuman/ (5402554)

46 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (6032953)

47 43 or 44 or 45 or 46 (94142)

48 exp human/ (19414037)

49 human experiment/ (399557)

50 48 or 49 (19415631)

51 47 not (47 and 50) (6649489)

52 42 not 51 (935041)

53 0959-8146.is. (59933)

54 (1469-493X or 1366-5278).is. (18038)

55 1756-1833.en. (24829)

56 53 or 54 or 55 (95436)

57 52 not 56 (928994)

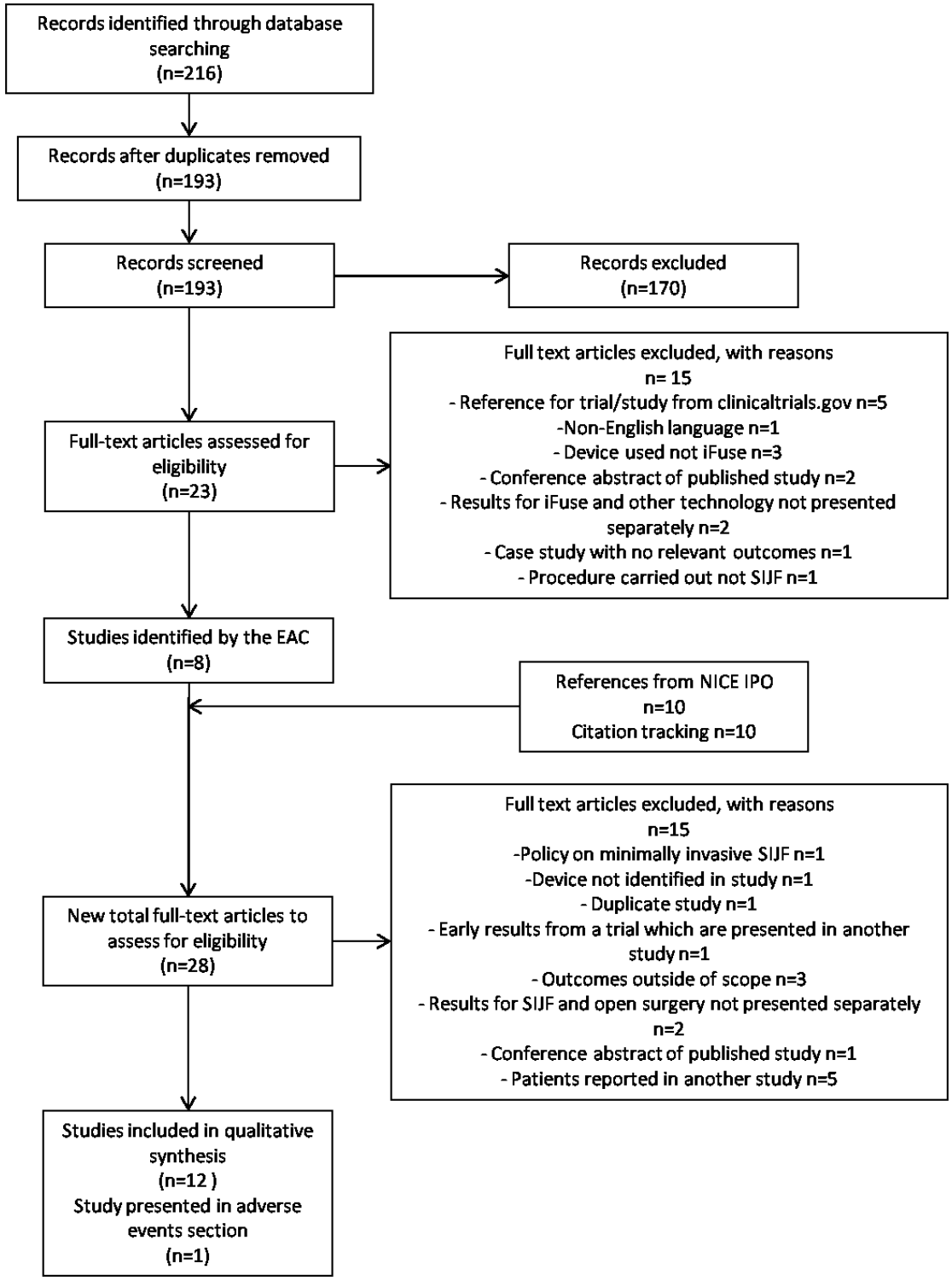
58 conference abstract.pt. (2798087)

59 57 not 58 (785203)

60 21 and 59 (20)

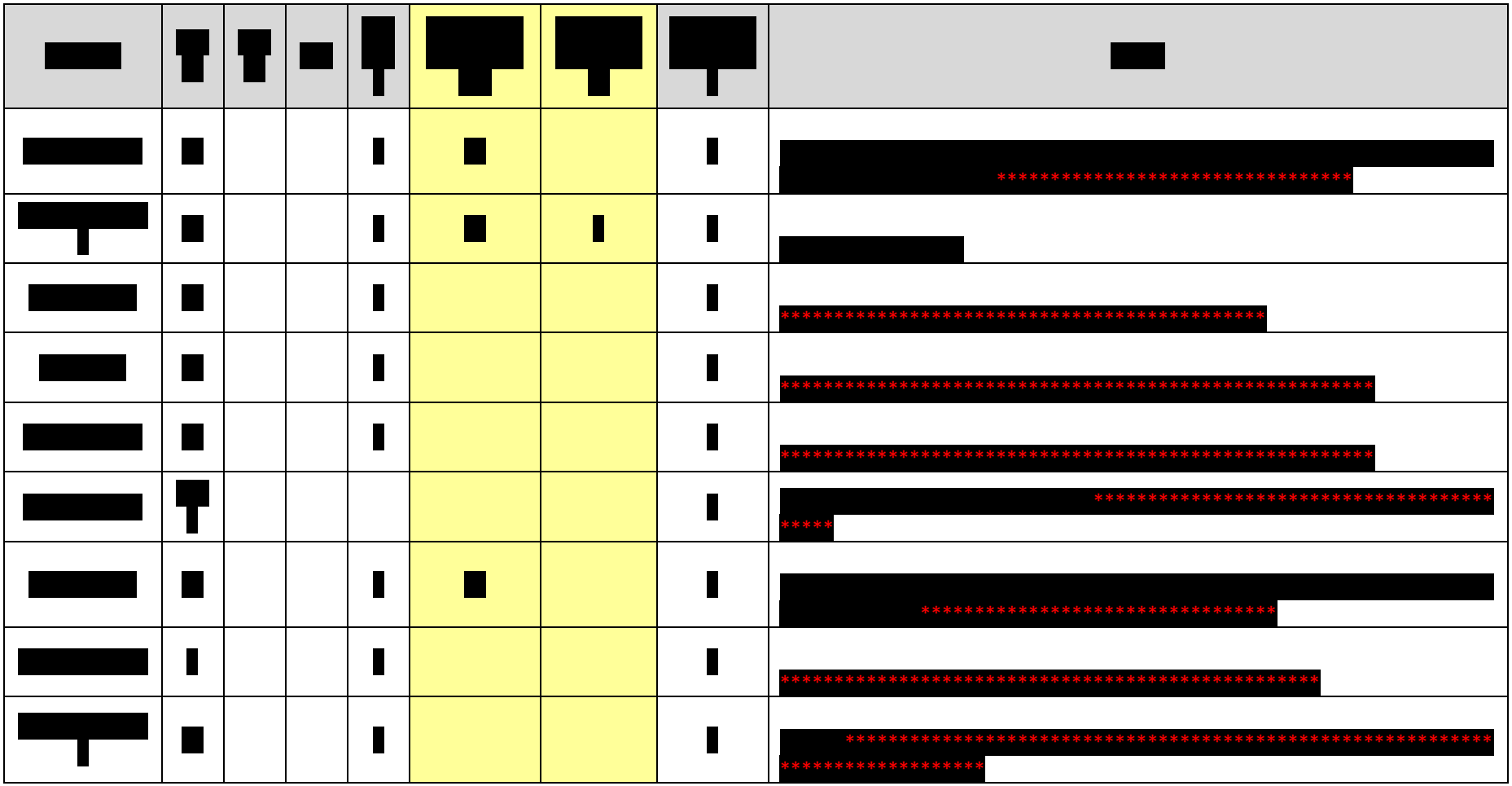
61 limit 60 (17)

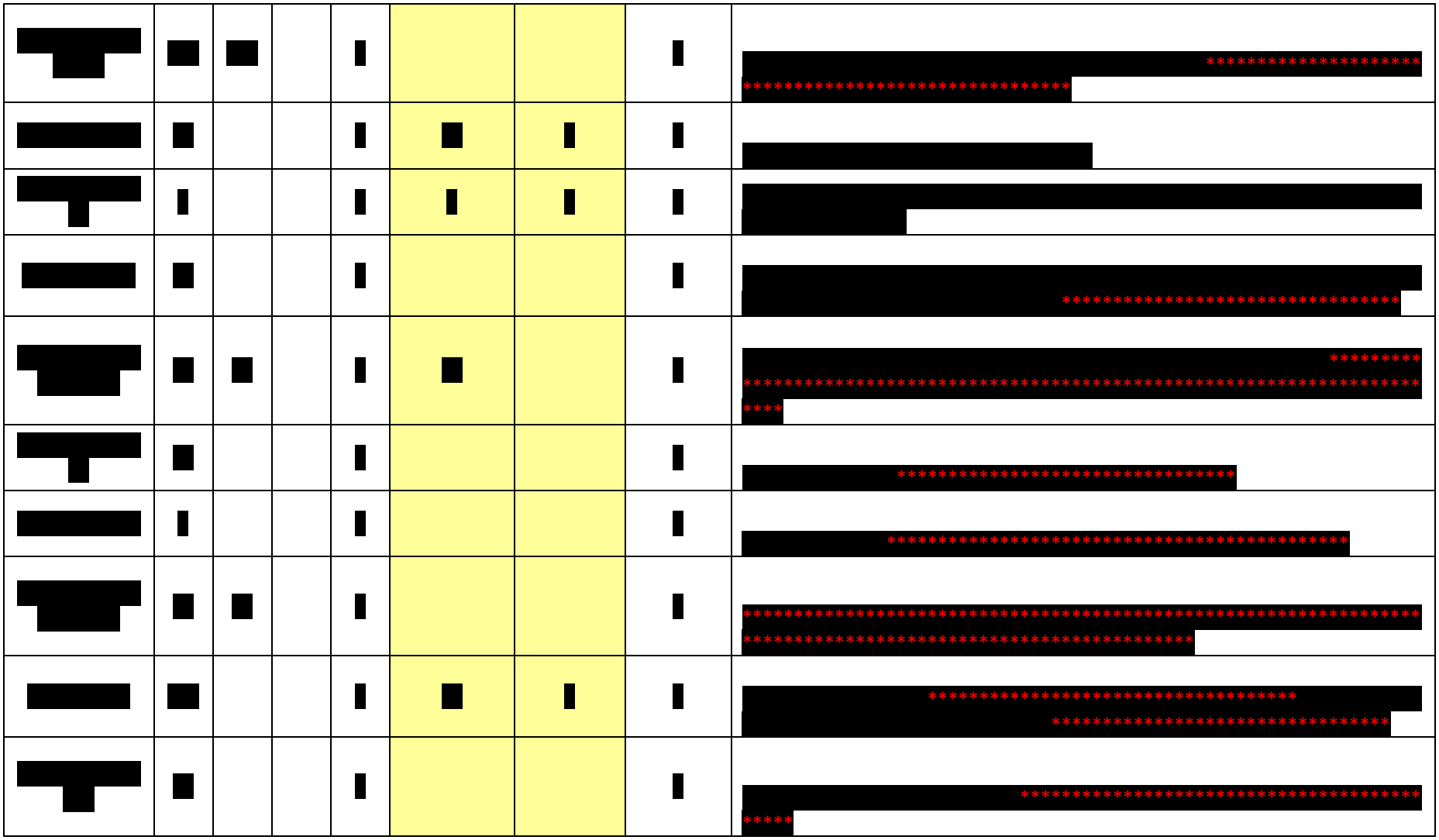
EAC PRISMA diagram

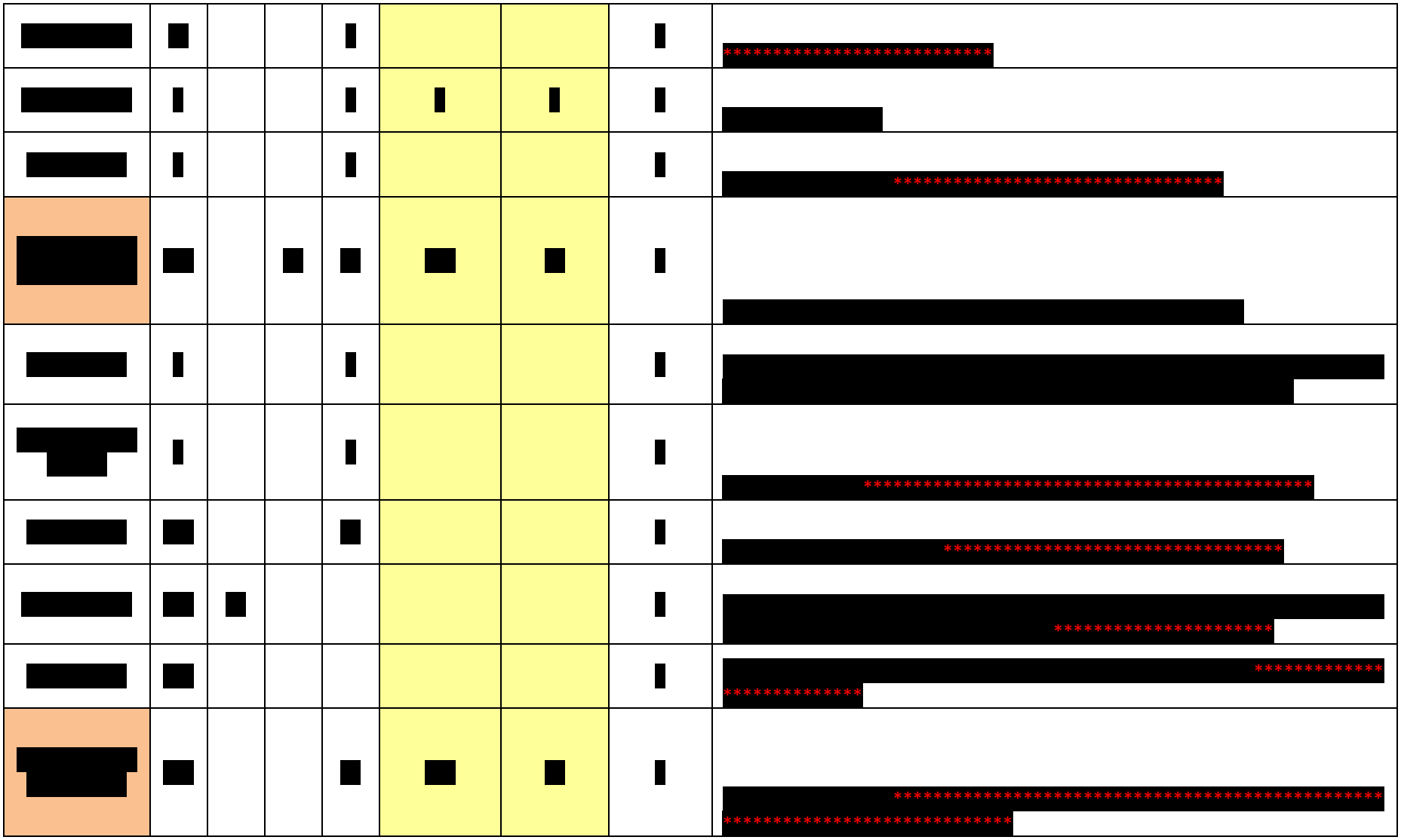


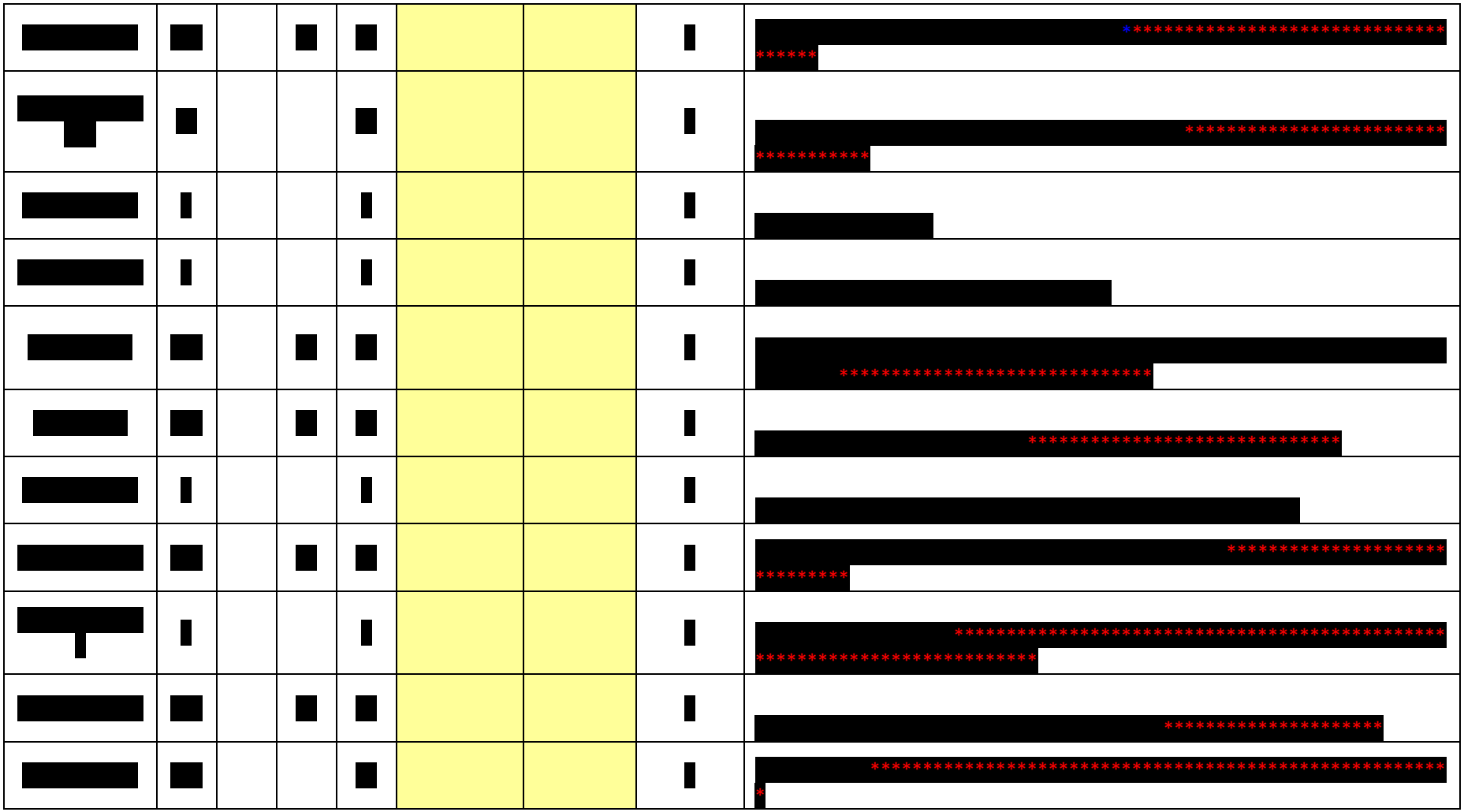
Appendix B – Patient origin for company submitted studies

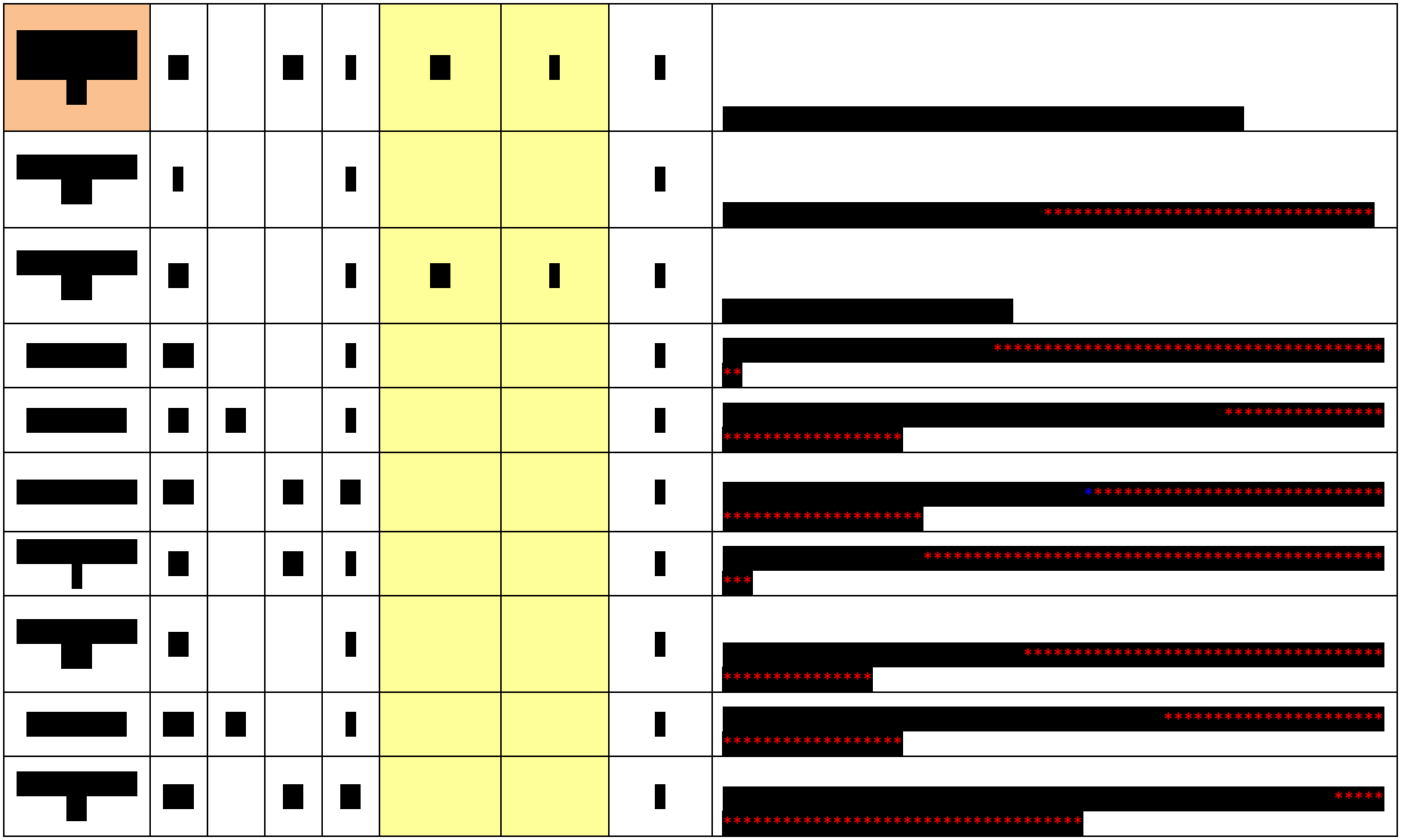
[redacted]











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[redacted]	[redacted]			[redacted]			[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]			[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]			[redacted]	[redacted]

Appendix C – EAC critical appraisal of included studies.

The critical appraisal checklists used below are produced by the Specialist Unit for Review Evidence (SURE). The following checklists were used:

- Specialist Unit for Review Evidence (SURE) 2016. Questions to assist with the critical appraisal of randomised controlled trials and other experimental studies available at: http://www.cardiff.ac.uk/insrv/libraries/sure/checklists.html
- Specialist Unit for Review Evidence (SURE) 2016. Questions to assist with the critical appraisal of a case series Available at: http://www.cardiff.ac.uk/insrv/libraries/sure/checklists.html
- Specialist Unit for Review Evidence (SURE) 2016. Questions to assist with the critical appraisal of cohort studies. Available at: http://www.cardiff.ac.uk/insrv/libraries/sure/checklists.html

Citation: Bornemann et al. (2017)		
Study Design: non-comparative, prospective study.		
1.	Does the study address a clearly focused question/hypothesis	Yes To report the outcomes of SIJF over 24 month follow up.
	Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	P: People with SIJ. I: iFuse. C: No comparator. O: Pain intensity, functional impairment, device and surgery-related adverse events, radiographic evidence of implants position. The primary outcome not specified.
2.	Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	No. This was a non-comparative study.
3.	Was allocation to intervention or comparator groups concealed? Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants	No. This was a non-comparative study.

	coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4.	Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	No. This was a non-comparative study.
5.	Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	No. The intervention was well described by the authors, however, the data was missing regarding the patients' previous treatment. There were no comparators (a non-comparative study).
6.	Was ethical approval sought and received? Do the authors report this?	Yes. The study was conducted with the principles laid in the Declaration of Helsinki. All patients gave their informed consent prior the first examination.
7.	Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	No.
8.	Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (e.g. age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable. This was a non-comparative study.
9.	Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Not applicable. This was a non-comparative study.
10.	Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Yes. All patients were followed-up for 24 months. Patients were not randomised as this was a non-comparative study.
11.	Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Yes. The statistical analysis was well described.
12.	Results Were outcome measures reliable (e.g. objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed?	Most of the results were subjective as they relied on patients' score using visual analogue scales and they feeling. Conclusions are adequately supported by the results.

	Are the authors' conclusions adequately supported by the results?	
13.	Is any sponsorship/conflict of interest reported?	Yes, the Conflict of interest statement is attached. No conflict of interest was reported by any of the authors.
14.	Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	No limitations were identified/reported by the authors. The conclusions are the same in the abstract and the full text.

Citation: Capobianco et al. (2015)	
Study Design: Sub-group analysis of a non-comparative, multi-centre, prospective study (see Duhon et al. 2016)	
1. Does the study address a clearly focused question/hypothesis	Yes To assess the safety and effectiveness of MIS SI joint fusion in a subgroup of patients with degenerative sacroiliitis and/or SI joint disruptions whose pain began in the peri-partum period
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	**Population:** People with SI joint dysfunction. **Intervention:** SIJF with iFuse. **Comparator:** No comparator. **Outcomes:** SIJ pain, quality of life, revision surgery and device-related adverse events. Yes. The primary endpoint was a binary success/failure composite endpoint at 6 months.
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	No. This was a non-comparative study. However, comparisons are carried out between 3 groups: women post-partum posterior pelvic girdle pain (PPGP), women with no PPGP and men.
3. Was allocation to intervention or comparator groups concealed? Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	No. This was a non-comparative study.

4.	Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	No. This was a non-comparative study.
5.	Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Yes. The intervention was well described by the authors. There were no comparators as this was a non-comparative study.
6.	Was ethical approval sought and received? Do the authors report this?	Yes. The study protocol was Institutional Review Board (IRB)-approved at each participating clinical site prior to patient enrolment.
7.	Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Yes. The study is part of the sacroiliac joint fusion with iFuse implant system (SIFI) trial. The trial protocol is available at: https://clinicaltrials.gov/ct2/show/NCT01640353. The outcomes listed in the protocol match those presented in the paper.
8.	Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (e.g. age, sex, social class, life style etc.)? Are any differences >10%?	This was a non-comparative study and therefore there were no treatment and comparator groups. However, there 3 sub-groups were analysed. Baseline characteristics were provided. Women with PPGP were significantly younger than women with no PPGP and men.
9.	Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Yes. The study's sample size has been discussed in the paper by Duhon et al. (2016) and is as follows: Enrolment into the study was stopped after 172 patients were enrolled and treated. No power calculation was included. However, the authors state that study sample size was determined using a pre-planned interim analysis.
10.	Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Not in this paper. However, according to the paper by Duhon et al. (2016) the percentage of patients followed-up was as follows: The percentage of patients followed-up at 6, 12 and 24 months was 97.1%, 91.3% and 86.6% respectively. This was a non-comparative study therefore patients were not randomised. This paper does not state how missing data were handled. However, the paper by Duhon et al. (2016) describes how missing data were

	handled: ITT analysis, using last observation carried forward, was used for the primary outcome only. All other analyses were per protocol. A table with results has been presented by the authors. The table presents the number of patients at each follow-up time-point for each patient reported outcome.
11. Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Not in this paper. However, the paper by Duhon et al. (2016) describes the following: The statistical methods have been well described. ITT analysis, using last observation carried forward, was used for missing data the primary outcome only. Per protocol analysis was used for all other data. Patients lost to follow-up were presented in a flow diagram.
12. Results Were outcome measures reliable (e.g. objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	The majority of the outcome measures are subjective as they ask the patients to score outcomes using visual analogue scales and their own feelings regarding pain, quality of life and satisfaction. The primary and the majority of secondary outcomes listed in the protocol have been assessed. The authors' conclusions do not fully reflect their results.
13. Is any sponsorship/conflict of interest reported?	Yes. The study was sponsored by SI-BONE. The two study authors are employees of SI-BONE.
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	The authors identified the following limitations: SIFI was not designed to diagnose PPGP; the number of subjects with PPGP was fairly low, limiting the ability to draw precise conclusions regarding differences in pain and QOL responses compared to the other subgroups; the study lacked a concomitant control group of women who received only non-surgical treatment. Conclusions in the abstract match those in the full text. However, as previously stated, the conclusions don't fully reflect their results.

Citation: Cher et al. (2015)

Are there other companion papers from the same study? No	
	No
1. Is the study design clearly stated? Consider if retrospective or prospective	No. However, the study is retrospective, non-comparative case series.
2. Does the study address a clearly focused question? Consider: population and outcomes (are these appropriate?)	Yes. The aim of the study is to perform the analysis of implant survivorship based on patients' complaints and to calculate the likelihood of revision surgery. P: Patients after SIJF which required a revision surgery. O: Revision rates.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; follow-up & data collection.	Yes. The authors stated that they used the data provided from two SI-BONE -maintained inventory management and complaints databases, however, the location of each SIJF was not specified. The data was collected from April 2009 to 15th July 2014.
4. Are there explicit inclusion/exclusion criteria?	Yes. Only patients with iFuse implants were included in the analysis. Index cases that were inconsistent with the device's labelled instructions for use were excluded prior to analysis.
5. Were patients enrolled consecutively?	Can't tell from the paper. However, the analysis was based on 11,820 patients who underwent SIJF over 6-year period, thus, it is unlikely that patients were enrolled consecutively.
6. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Yes. Information about patients' age, sex, year of SIJF and number of implants after SIJF is provided in the table. Lack of more detailed patient characteristics.
7. Are outcome measures appropriate? Consider if: the methods of assessment are valid & reliable.	Yes. Each patient' complaint was manually reviewed and classified according to whether or not it represents a surgical revision. When further

	information was required, the specialist was contacted. Each revision case was manually linked to the corresponding index surgery in the company database.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. Five complains, which were not linked to SIJF surgery, were excluded from the analysis.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Yes. Flow diagram was not prepared, but information about excluded patients was provided. Detail information about the year of SIJF surgery, number of implants after SIJF and the reason for revision was provided.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the results support the conclusions and are they the same in the abstract and the full text.	Yes. The results are well described, however, confidence intervals/standard deviations are not provided. The results support the conclusions.
11. Is any sponsorship/conflict of interest reported?	Yes. All authors are SI-BONE employees.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. Authors list several limitations: lack of the data of other patient factors (e.g. BMI), not all revisions were linked to index surgeries, possibility that not all surgeries were reported to the company, the analysis did not include death due to other causes, the procedures other than SI joint revision were not included. Yes, the lack of more detailed patient characteristics was captured in Q6.

Citation: Dengler et al. (2017b)	
Study Design: Multi-centre, open-label RCT.	
1. Does the study address a clearly focused question/hypothesis	Yes The study reports the 12 month results from a multicenter RCT comparing clinical outcomes of minimally invasive SIJF vs. CM

		for patients with chronic SIJ pain.
	Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	**Population:** Patients with chronic SIJ pain. **Intervention:** minimally invasive SIJF using iFuse. **Comparator:** conservative management (CM) derived from European guidelines, consisted of 1) optimization of medical therapy, 2) individualized physiotherapy (PT) at least twice per week for up to 8 weeks that focused on mobilization and stabilization exercises for control and stability, and 3) adequate information and reassurance for the patient as part of a multi-factorial treatment. **Outcomes:** Low back pain (LBP) improvement at 6 and 12 months, LBP improvement at 12 months, Oswestry disability index (ODI) at 12 months, SIJ function, EQ-5D TTO and EQ-5D VAS at 12 months, SIJ function, patient depression, patient satisfaction, adverse events and leg pain. Yes, the primary outcome was the difference in self-related LBP at 6 months.
2.	Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	Yes. Patients were assigned at random in a 1:1 ratio after eligibility and baseline assessments (see below) by study coordinators using a password-protected website. Randomisation sequences were computer-generated using a random number generator. Randomisation was stratified by site and pregnancy-relatedness of SIJ pain, with random block sizes of 4 or 6.
3.	Was allocation to intervention or comparator groups concealed? Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	Unclear. There is no mention of who carried out the allocation.
4.	Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	No. Patients and researchers were not blinded to treatment. This would be difficult in this case

	as one study group received a surgical treatment and the other received non-surgical treatment. Assessment of outcomes was not blinded.
5. Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Yes. Both groups received follow-up appointments at the same intervals. Exposure was adequate. Patients treated with CM were permitted to cross-over to SIJF treatment with iFuse or any other surgical or interventional procedure if they felt they had not derived benefit from CM after 6 months. These patients were not permitted cross-over before 6 months.
6. Was ethical approval sought and received? Do the authors report this?	Yes. The study protocol was approved at all sites by ethics committees prior to first patient enrolment.
7. Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Yes. The study is part of the iFuse Implant System Minimally Invasive Arthrodesis (iMIA) trial. The trial protocol is available at: https://clinicaltrials.gov/ct2/show/NCT01741025. Outcomes presented in the paper have been presented in the trial protocol.
8. Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (e.g. age, sex, social class, life style etc.)? Are any differences >10%?	Yes. Baseline characteristics have been presented in a table. Patients were similar in both groups for all characteristics presented apart from smoking history. The SIJF group had a significantly higher number of smokers (current and former) than patients in the CM group.
9. Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Yes. There were enough participants. There was a power calculation. The study's target sample size (40 per group) provided 80% power to detect a difference of 20 points in VAS SIJ pain assuming a standard deviation (SD) of 35 points. The SIJF group had 52 patients and the CM had 51 patients. Due to patients in the CM group being permitted to "cross-over" to surgical treatment after 6 months, the numbers of patients receiving CM treatment after 6 months was reduced from 49 to 28 patients.
10. Were participants properly accounted for? Was follow-up ≥ 80%?	Yes. The 12 month follow-up rate was 92%.

	Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Patients were analysed in the groups to which they were randomised in part. Patients in the CM group were allowed to "cross-over" to surgical care after 6 months if they were not benefitting from CM. These patients were then analysed in a "cross-over" group. Intention to treat was conducted by using last observation carried forward to replace missing data from those patients who were moved to the "cross-over" group.
11.	Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Yes. Primary and secondary study endpoints have been presented. Because crossover to surgical treatment prevented assessment of 12-month responses to CM alone, the last-observation carry forward (LOCF) imputation method was used to estimate 12-month values for CM patients who crossed over. Confounding factors were controlled for through randomisation. Both groups were similar in terms of baseline characteristics except for history of smoking; this was significantly higher in the SIJF group. Patients lost to follow-up were presented in a flow diagram.
12.	Results Were outcome measures reliable (e.g. objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	The majority of the outcome measures are subjective as they ask the patients to score outcomes using visual analogue scales and their own feelings regarding pain, impact on life and the treatment received. All outcomes listed by the author as primary and secondary outcomes were assessed. The authors' conclusions are adequately supported by the results.
13.	Is any sponsorship/conflict of interest reported?	Yes. The study was sponsored by SI-BONE (the manufacturer). The sponsor provided tools for electronic data capture. Study authors' practices or universities were paid by the sponsor to support the research (supplies, personnel, etc.). The sponsor helped to perform data monitoring, source verification, cleaning and statistical analysis. All statistical analysis was reviewed by study authors. The sponsor prepared an initial draft of the study manuscript. Daniel Cher is an SI-BONE employee. Eddie van Eeckhoven is a clinical trials and regulatory consultant to SI-BONE. Bengt Sturesson, Djaya Kools and Robert Pflugmacher are paid consultants to SI-BONE.

	No author received direct payment for the study. No author has received any reimbursement or honorarium in any other manner.
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	The authors identified the following limitations: the intervention was not blinded, it is possible that extraneous factors associated with SIJF may have contributed to greater responses in the SIJF group; while the diagnostic algorithm used was standardized, it is possible that some patients had other pathologies contributing to LBP, which could have limited the degree of response to SIJF; non-surgical care, patterned after European guidelines for pelvic girdle pain, may have varied across centres; the fact that a substantial number of patients undergoing CM crossed over to surgery after 6 months prevented direct effect size calculations after the month 6 visit.

Citation: Duhon et al. (2016)	
Study Design: Non-comparative, multi-centre, prospective study.	
1. Does the study address a clearly focused question/hypothesis	Yes To report the 24 month outcomes from a prospective multi-centre clinical trial on SIJF.
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	**Population:** People with SI joint dysfunction. **Intervention:** SIJF with iFuse. **Comparator:** No comparator. **Outcomes:** SIJ pain, quality of life, opioid use, revision surgery, device-related adverse events, bone adherence to the implant, ambulatory and work status. Yes. The primary endpoint was a binary success/failure composite endpoint.
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	No. This was a non-comparative study.
3. Was allocation to intervention or comparator groups concealed? Is it possible for those allocating to know which group they are allocating people to?	No. This was a non-comparative study.

	As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	
4.	Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	No. This was a non-comparative study.
5.	Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Yes. The intervention was well described by the authors. There were no comparators as this was a non-comparative study.
6.	Was ethical approval sought and received? Do the authors report this?	Yes. The study protocol was Institutional Review Board (IRB)-approved at each participating clinical site prior to patient enrolment.
7.	Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Yes. The study is part of the sacroiliac joint fusion with iFuse implant system (SIFI) trial. The trial protocol is available at: https://clinicaltrials.gov/ct2/show/NCT01640353. The outcomes listed in the protocol match those presented in the paper.
8.	Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (e.g. age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable, this was a non-comparative study. A baseline characteristic table has been presented by the manufacturer.
9.	Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Yes. Enrolment into the study was stopped after 172 patients were enrolled and treated. No power calculation was included. However, the authors state that study sample size was determined using a pre-planned interim analysis.
10.	Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Yes. The percentage of patients followed-up at 6, 12 and 24 months was 97.1%, 91.3% and 86.6% respectively. This was a non-comparative study therefore patients were not randomised. ITT analysis, using last observation carried forward, was used for the primary outcome only. All other analyses were per protocol.
11.	Data analysis Are the statistical methods well described? Consider: How missing data was handled; were	Yes. The statistical methods have been well described.

potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	ITT analysis, using last observation carried forward, was used for missing data the primary outcome only. Per protocol analysis was used for all other data. Patients lost to follow-up were presented in a flow diagram.
12. Results Were outcome measures reliable (e.g. objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	The majority of the outcome measures are subjective as they ask the patients to score outcomes using visual analogue scales and their own feelings regarding pain, quality of life and satisfaction. All primary and secondary outcomes listed in the protocol have been assessed. The authors' conclusions are adequately supported by the results.
13. Is any sponsorship/conflict of interest reported?	Yes. The study was sponsored by SI-BONE. Three of the authors are paid consultants to SI-BONE. One of the authors is an employee of SI-BONE.
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	The authors identified the following limitations: Lack of a concurrent control group undergoing non-surgical treatment, a 24-month follow-up rate that was not as high as desired. Conclusions in the abstract match those in the full text.

Citation: Miller et al. (2015) *Are there other companion papers from the same study?*	
	No
1. Is the study design clearly stated? Consider if retrospective or prospective	No. However, the study is a retrospective, non-comparative case series.
2. Does the study address a clearly focused question? Consider: population and outcomes (are these appropriate?)	Yes. The aim of the study was to provide a detailed characterization of complaints reported with the iFuse system by performing an evaluation and analysis of the manufacturer's post-market complaints database. Population: people with SIJ with SIJ disruption or degenerative sacroiliitis who received SIJF using iFuse.

3. Are the setting, locations and relevant dates provided? Consider: recruitment period; follow-up & data collection.	Yes. The patient were treated between April 2009 and January 2013, 5319 patients in the US (n = 4962) and Europe (n = 357). The method of data collection has been described by the authors.
4. Are there explicit inclusion/exclusion criteria?	No.
5. Were patients enrolled consecutively?	There is no way to tell from the paper. However, this seems unlikely as this paper presents post-market surveillance of post-procedural complaints across sites in Europe and the USA.
6. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	No. The study does not present any participant characteristics. It is likely that the database which holds patient complaints does not collect demographic information on the patient with the complaint.
7. Are outcome measures appropriate? Consider if: the methods of assessment are valid & reliable.	Yes. The authors have presented tables with a breakdown of the different type of complaint, what the complaint was and also the reason for revision when this was carried out.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	No statistical methods were used. The authors have presented complaints in a table.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	No. The authors state that there were 5,319 patients treated with iFuse and that complaints were reported in 204 patients.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the results support the conclusions and are they the same in the abstract and the full text.	The results are described as well as they could be. It is likely that the database used to inform this study only collects some key information and is not exhaustive. The results have been presented in tables with clear headings and sub-groups where appropriate. There wasn't a need for CIs or SDs as no means/medians have been presented.
11. Is any sponsorship/conflict of interest reported?	The study was supported in part by SI-BONE. The authors declare no other conflicts of interest in the work. However, one of the study authors is an employee of SI-BONE.

12. Finally…Did the authors identify any limitations and, if so, are they captured above?	The authors listed the following limitation: Spontaneous complaint reporting may underestimate the true incidence of events. While the extent of possible complaint under-reporting is unknown, it is plausible that the true rate of complaints with the iFuse system is higher than that reported in the current study. The authors did not mention the weaknesses in the study identified and presented above.

Citation: Polly et al. (2016b).	
Study Design: Mutli-centre, open label RCT	
1. Does the study address a clearly focused question/hypothesis	Yes The study reports the 24 month results of a study which prospectively and concurrently compares outcomes after surgical and non-surgical treatment for chronic SIJ dysfunction.
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	**Population:** patients with chronic SIJ dysfunction **Intervention:** minimally invasive SIJF using iFuse. **Comparator/control:** non-surgical management (NSM) consisting of pain medications, physical therapy, intraarticular SIJ steroid injections and radiofrequency (RF) ablation of lateral branches of the sacral nerve roots. Therapy was delivered in a stepwise fashion to address pain and disability according to each individual's needs. **Outcomes:** Pain score improvement, ODI and EQ-5D at 6, 12 and 24 months, patient satisfaction, opioid use, adverse events, revision surgeries, predictors of SIJF and NSM success. Yes, the primary outcome was the primary study endpoint, evaluated at 6 months after the most recent SIJF (to accommodate subjects with planned staged bilateral surgery), was a binary success/failure composite measure.
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes	Yes. Randomisation was stratified by site and underlying diagnosis (degenerative sacroiliitis

	Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	or SIJ disruption) in a 2:1 ratio to either SIJF or NSM with randomly chosen block sizes of 6 or 9. Randomization sequences were computer-generated and obtained via a password protected study website.
3.	Was allocation to intervention or comparator groups concealed? Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	Unclear. There is no mention of who carried out the allocation.
4.	Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	No. Patients and researchers were not blinded to treatment. This would be difficult in this case as one study group received a surgical treatment and the other received non-surgical treatment. Assessment of outcomes was not blinded.
5.	Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Yes. Both groups received follow-up appointments at the same intervals. Exposure was adequate. Patients treated with NSM were permitted to cross-over to surgical SIJF treatment if they felt they had not derived benefit from NSM after 6 months. These patients were not permitted cross-over before 6 months.
6.	Was ethical approval sought and received? Do the authors report this?	Yes. Local or regional institutional review boards approved the study. All patients provided study-specific informed consent prior to participation.
7.	Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	Yes. This study is part of the Investigation of Sacroiliac Fusion Treatment (INSITE) trial. The trial protocol is available at: https://clinicaltrials.gov/ct2/show/NCT01681004. Outcomes presented in the paper have been presented in the trial protocol.
8.	Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (e.g. age, sex, social class, life style etc.)?	Yes. Baseline characteristics have been presented in a table in the paper. Patients in both

	Are any differences >10%?	groups were similar for all characteristics presented apart from smoking status. The SIJF group had a significantly higher number of current smokers than the NSM group.
9.	Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Uncertain. It is uncertain if there were enough participants as there was no power calculation. Due to patients in the NSM group being permitted to "cross-over" to surgical treatment after 6 months, the numbers of patients receiving NSM treatment after 6 months was hugely reduced from 49 to 5 patients.
10.	Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Yes. Follow-up in the SIJF group was 87.3% at 24 months. However, due to cross-over, follow-up for the NSM group was ~10% at 24 months. Patients were analysed in the groups to which they were randomised in part. Patients in the NSM group were allowed to "cross-over" to surgical care after 6 months if they were not benefitting from NSM. These patients were then analysed in a "cross-over" group. Intention to treat analysis was used for the 6 month primary endpoint only. It appears per protocol analysis was used thereafter.
11.	Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	In part. The statistical methods used have been adequately described. The authors have described how missing data was handled up to 6 months, where an intention to treat approach was used. However, there is little information on how missing data were handled after 6 months. It is implied that per protocol analysis was used thereafter. However, this is not explicitly described. Confounding factors were controlled for through randomisation. Both groups were similar in terms of baseline characteristics except for history of smoking; this was significantly higher in the SIJF group. Patients lost to follow-up were presented in a flow diagram.
12.	Results Were outcome measures reliable (e.g. objective or subjective measures)? Were all outcome measurements complete?	The majority of the outcome measures are subjective as they ask the patients to score outcomes using visual analogue scales and their own feelings regarding pain, satisfaction

	Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	and impact on life. All outcomes listed by the author as primary and secondary outcomes were assessed. The authors' conclusions are adequately supported by the results.
13.	Is any sponsorship/conflict of interest reported?	Yes. The study was sponsored by SI-BONE (the manufacturer). Two of the study authors are paid consultants to SI-BONE. Two of the study authors are employees of SI-BONE. The study manuscript was written jointly by the authors and SI-BONE; statistical analyses were completed by SI-BONE.
14.	Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	The authors identified the following limitations: The sample size for NSM was small due to patients moving to the "cross-over" group. The conclusions in the text differ from those in the abstract to some degree. The abstract conclusions appear to be more specific than those in the text. However, the conclusions in the text discuss implant revision rate whilst the conclusions in the abstract do not.

Citation: Rudolf and Capobianco (2014)	
Study Design: Prospective, non-comparative study	
1. Does the study address a clearly focused question/hypothesis	Yes To report on long-term (5 year) clinical outcomes in patients treated with SIJF.
Population/Problem? Intervention? Comparator/control? Outcomes? Can you identify the primary outcome?	Population: people with degenerative sacroiliitis and/or SI joint disruptions. Intervention: SIJF using iFuse. Comparator: none. Outcomes: Pain and patient satisfaction at baseline, 12, 24 and 60 months, health-related quality of life at baseline, 12 and 60 months, disability at 60 months, adverse events, SI joint health related outcomes, radiographic evidence.
2. Was the population randomised? If YES, were appropriate methods used? Eg: random number tables, opaque envelopes Note: The following methods are not appropriate: alternating participants coin toss, birth dates, record numbers, days of the week	No, this was a non-comparative study.

3.	Was allocation to intervention or comparator groups concealed? Is it possible for those allocating to know which group they are allocating people to? As above, methods such as alternating participants coin toss, birth dates, record numbers, days of the week will not allow appropriate allocation concealment.	Not applicable, this was a non-comparative study.
4.	Were participants/investigators blinded to group allocation? If NO, was assessment of outcomes blinded?	Not applicable, this was a non-comparative study.
5.	Were interventions (and comparisons) well described and appropriate? Aside from the intervention, were the groups treated equally? Was exposure to intervention and comparison adequate? Was contamination acceptably low?	Yes. The intervention was well described. There was no comparator as this was a non-comparative study.
6.	Was ethical approval sought and received? Do the authors report this?	Unclear. The authors state that the patients signed an IRB-approved consent form before beginning any study related activity. There is no other mention of how ethical approval was obtained.
7.	Was a trial protocol published? Was a protocol published in a journal or clinical trial registry before participants were recruited? If a protocol is available, are the outcomes reported in the paper listed in the protocol?	There does not appear to be a published protocol.
8.	Were the groups similar at the start of the trial? Are baseline characteristics provided and discussed (e.g. age, sex, social class, life style etc.)? Are any differences >10%?	Not applicable, this was a non-comparative study.
9.	Was the sample size sufficient? Were there enough participants? Was there a power calculation? If YES, for which outcome? Were there sufficient participants?	Uncertain. There was no power calculation and the authors do not state that enough participants were recruited.
10.	Were participants properly accounted for? Was follow-up ≥ 80%? Were patients analysed in the groups to which they were randomised? Was an Intention to Treat analysis conducted? Was the follow-up period long enough?	Follow-up was >80%. No ITT was carried out.
11.	Data analysis Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was	Yes. The statistical methods were described with enough details (the programme used and calculations of p values).

addressed.	
12. Results Were outcome measures reliable (e.g. objective or subjective measures)? Were all outcome measurements complete? Were all important outcomes assessed? Are the authors' conclusions adequately supported by the results?	The majority of the outcome measures were subjective as patients are asked to report pain, disability, satisfaction and quality of life. ODI was only collected at the 5 year follow-up and therefore no comparisons between baseline and other time-points can be made. The questionnaire used was created by the authors by combining components from the SF-36 and ODI. It therefore has not been validated. The authors' conclusions are adequately supported by the results.
13. Is any sponsorship/conflict of interest reported?	Yes. One of the authors is an SI-BONE investor, consultant and clinical trial investigator. The other author is an employee of SI-BONE. An employee of SI-BONE provided statistical advice. The study is sponsored by SI-BONE.
14. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Yes, the authors identified the following limitations: The study sample size was relatively small and ODI was only available at the 5-years, a comparison to baseline could not be performed. The conclusions in the abstract and the full text are the same.

Citation: Sachs et al. (2016) *Are there other companion papers from the same study?* Patients in this study were previously presented in Sachs and Capobianco (2013) and Sachs et al. (2014).	
	Yes
1. Is the study design clearly stated? Consider if retrospective or prospective	Yes. The authors state that the study is a retrospective cohort study with a prospective evaluation component. However, the study is a retrospective case series.
2. Does the study address a clearly focused question? Consider: population and outcomes (are these appropriate?)	Yes. Population: People with SIJ dysfunction. Outcomes: SIJ pain, ODI, patient satisfaction and revision rates.

	The outcomes are appropriate.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; follow-up & data collection.	In part. The recruitment period was prior to December 2012. The mean follow-up period was 3.7 years and the data collection has been described.
4. Are there explicit inclusion/exclusion criteria?	No. No exclusion criteria have been presented. The only inclusion criteria listed are adults (at least 21 years) who underwent SIJF with iFuse prior to December 2012.
5. Were patients enrolled consecutively?	Yes.
6. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Yes. Patient characteristics have been presented in a table. However, the authors have not included information on gender.
7. Are outcome measures appropriate? Consider if: the methods of assessment are valid & reliable.	In part. The main outcomes are subjective as the patients score themselves. The questionnaire used to assess pain does not appear to be validated. The number of revisions required has been presented and this appears valid and reliable.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	In part. A brief overview of the statistical methods used has been presented. The authors state that some patients did not participate. The authors appear to have presented results for patients who completed surveys. Confounding factors have not been considered. The authors could have given some demographic information on the non-responders to determine if there were differences between responders and non-responders.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	No. The authors haven't included a flow diagram. The authors state that only patients who returned their questionnaires were included. However, the number of people who did not return the questionnaires was not presented. The authors have presented a mean follow-up time.

10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the results support the conclusions and are they the same in the abstract and the full text.	In part. Results have been presented in tables. Mean and standard deviation have been presented for SIJ pain and ODI. Other outcomes have been presented in box-plots. However, the authors have not included a description of what the box-plot represents. The conclusions are the same in the abstract and full-text.
11. Is any sponsorship/conflict of interest reported?	Yes. The study was sponsored by manufacturer (SI-BONE). Two of the authors are consultants to SI-BONE. All of the authors conduct clinical research for SI-BONE-sponsored clinical trials. However, the authors report no other conflicts of interest in the study. Patients received a nominal payment for taking part in the study.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The authors reported the following limitations: Our study was retrospective by design and could be subject to biases inherent in this design; some patients did not participate because of inability to make contact or patient refusal; methods to diagnose SIJ pain may have varied across sites and time; not all patients in our cohort underwent physical therapy; baseline ODI scores were not available in most patients, limiting our ability to determine per patient improvements in this commonly reported parameter; we did not perform standardized long-term imaging of the SIJ; many patients in our cohort had concomitant spine disease at baseline and a substantial fraction underwent other spine surgeries or interventional spine or hip procedures, such interventions may have limited improvements in ODI or affected patients' abilities to perform activities of daily living. The limitations identified by the authors have been captured above.

Citation: Schroeder et al. (2013)

Are there other companion papers from the same study?	
	No
1. Is the study design clearly stated? Consider if retrospective or prospective	Yes. The authors clearly stated that the study is a retrospective review.
2. Does the study address a clearly focused question? Consider: population and outcomes (are these appropriate?)	Partially. The aim of the study was to report outcomes of the SIJF after 24 months of follow-up in patients from a single specialised scoliosis centre (centre not specified). P: People with SIJ after a long spine fusion. O: improvement in pain and function, patient HRQoL, radiographic evidence, postoperative complications, length of hospital stay.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; follow-up & data collection.	Yes. The patients were treated in a single specialised scoliosis centre. SIJF was performed between 2011 – 2013. Patients were followed in the outpatient deformity clinic post-operatively at 2 and 6 weeks, 3 and 6 months, and 1 and 2 years after the procedure.
4. Are there explicit inclusion/exclusion criteria?	Yes. Patients who underwent open SIJ fusion or did not undergo a long spine fusion (over six motion segments) ending at the sacrum were excluded from the study.
5. Were patients enrolled consecutively?	Can't tell from the paper. However, this seems very likely as only 6 patients were reported and were recruited over 2 year period.
6. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Yes. Very basic characteristics are provided: age, sex, previous spine fusion details, SIJF.
7. Are outcome measures appropriate? Consider if: the methods of assessment are valid & reliable.	Yes. The authors used commonly used questionnaires (VAS, ODI, and SRS22) and radiographic evidence (x-rays and CT scans) to assess the outcome.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. The statistical methods were described briefly, but with sufficient amount of details.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs;	The number of patients was the same as the study was retrospective case series.

details of missing participant data; follow-up time summarised; numbers of outcome events.	The data for each follow-up time-points was missing and summarised as pre- and post-operative.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the results support the conclusions and are they the same in the abstract and the full text.	The outcome measures were highly subjective – the authors used questionnaires or visual analogue scales. Instead of standard deviation/confidence intervals the authors used minimal clinically important difference (MCID). Not all outcome measures were complete. The authors collected the data at six different time-points; however, they reported VAS, ODI and SRS22 scores only pre- and post-intervention. No detail information was reported for the amount of days patient spent in the hospital.
11. Is any sponsorship/conflict of interest reported?	Yes. One author reported personal fees from DePuy and J&J. Two authors received grants from DePuy Synthes Spine during the conduct of the study. One receives grants from K2M, OsteoTech and Trans1 as well. One author is a consultant for DePuy, K2M, OsteoTech, and Trans1. One author received travel expenses and research support from K2M, outside the submitted work. One author has a patent and receives royalties from patents from DePuy and K2M.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The authors highlight the retrospective nature of the study, its short duration, small number of patients enrolled and a single reviewer of radiographic images as limitations.

Citation: Spain and Holt (2017) *Are there other companion papers from the same study?*	
	No
1. Is the study design clearly stated?	No. However, the study is a retrospective comparison between SIJF with iFuse and SIJ fixation using screws.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Comparator/Control; Outcomes.	Yes. Population: Patients with SIJ dysfunction. Exposure: SIJF with iFuse

	Comparator: SIJ fixation with screws Outcomes: number of revisions/revision rate.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; follow-up & data collection.	In part. No recruitment period has been stated. However, the setting has been noted. This was a single spine centre in the USA. Both exposure and comparator have been adequately described. Follow-up and data collection have been adequately described.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants; method of follow-up; for matched studies – details of matching criteria and number of exposed or unexposed.	Uncertain. The authors have not stated any eligibility criteria apart from patients needing to be at least 19 years old. The authors state that patients were identified through manual review and querying office billing databases. Patients were followed up through a review of clinic charts and telephone.
5. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Yes. The authors have included a simple table which presents age, BMI, gender, underlying cause of SIJ dysfunction and year of surgery. Patients undergoing SIJF with iFuse were significantly older than patients undergoing SIJ fixation with screws.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	The exposure and outcome are appropriate. The numbers of revisions needed were obtained from patient clinical notes.
7. Was bias considered? e.g. recall or selection bias	Bias was considered. Recall bias is reduced as medical notes were used to obtain information in revisions. However, participants were also contacted by telephone and asked if they had undergone surgical intervention by a physician other than the study author. This could have introduced some recall bias. There also may be bias as the mean follow-up time was longer for the SIJ fixation (with screws) than the SIJF with iFuse group. This could have an impact on the number of revisions observed in each group.
8. Is there a description of how the study size was arrived at?	Yes. The authors have described how the study size

	was arrived at.
9. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) controlled for; How loss to follow-up was addressed.	Yes. The authors have described the statistical methods used. Analysis into the effect of demographic factors on SIJ revision was carried out to determine if these had an effect on the likelihood of surgical revision.
10. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Yes. A flow diagram has been presented y the authors. The numbers of outcome events and a summary of follow-up time have been presented.
11. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. The results are simplistic. Ranges have been presented alongside means for baseline characteristics. The conclusions presented in the abstract are the same as those presented in the full text.
12. Is any sponsorship/conflict of interest reported?	Yes. The study was sponsored by SIBONE. SI-BONE staff helped with statistical analysis. Dr. Tim Holt is a consultant to SI-BONE.
13. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The authors identified the following limitations: Follow-up in the TTI group was shorter than in the SIJ fixation group, primarily because the TTI group was operated on more recently; not all SIJF with iFuse patients have 4-year follow-up, so the 4-year revision rate is potentially subject to change; the authors could not contact locate charts for some patients, potentially introducing a bias; we could not contact a small number of patients and it is possible that patients who could not be contacted underwent revision surgery however, no other surgeon local to our practice performs such procedures; the time periods for the two groups differ, suggesting that temporal factors, such as surgeon learning curve, changes in OR policies, or postoperative care regimens, could play a role. Te majority of the limitations have been captured above.

Citation: Vanaclocha et al (2018) *Are there other companion papers from the same study?*	
	Yes. **Vanaclocha et al. (2014)**
1. Is the study design clearly stated? Consider if retrospective or prospective	Yes, it is very clearly stated. The study is a comparative and retrospective case series.
2. Does the study address a clearly focused question? Consider: population and outcomes (are these appropriate?)	Yes. The aim of the study is to compare the outcomes (pain level, functional disability and pain medication use) in patients which had SIJF, sacroiliac denervation or CM over available follow-up period.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; follow-up & data collection.	Yes. The data was collected in a single centre (Department of Neurosurgery, Valencia, Spain) between January 2007 and November 2015. Unfortunately, not all patients had the same duration of the follow-up. The mean follow-up time was 4 years.
4. Are there explicit inclusion/exclusion criteria?	Yes. Patients were excluded if they had severe residual pain due to other causes than osteoarthritic degeneration, joint disruption; patients that had other sacroiliac pathology (trauma, fracture, tumour, 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. Patients were excluded if duration of follow-up was <12 months following SIJ pain diagnosis.
5. Were patients enrolled consecutively?	Can't tell from the paper. Patients were enrolled in single centre over long period of time.

6. Are participant characteristics provided? Consider if: sufficient details; a baseline table is included.	Yes. The patients characteristics are presented in the table which include age, sex, BMI, the number of patients that were smoking (including the amount of cigarettes per day). The authors included the primary underlying cause, pain location and duration, activities that worsen pain.
7. Are outcome measures appropriate? Consider if: the methods of assessment are valid & reliable.	Yes. The outcome measures are subjective as the authors used VAS and ODI scores, however, those questionnaires are widely used to assess pain level and patients' disability.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. The statistical methods are well described, including tests and software used.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; follow-up time summarised; numbers of outcome events.	Yes. The authors included a highly detailed flow diagram. Moreover, all the information about patient numbers at each stage and the reasons for drop-outs are provided. Follow-up time for each patient group is well summarised.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the results support the conclusions and are they the same in the abstract and the full text.	Yes. The results are well described and supported by the included graphs/tables. The results support the conclusions and do not differ between the abstract and the full text.
11. Is any sponsorship/conflict of interest reported?	No. The authors have no personal, financial or institutional interests in any of the drugs, materials or devices described in this article.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The authors point out that the study is not randomised, however, it is a retrospective study. Some patients could not receive SIJF or sacroiliac denervation due to lack of insurance coverage. Not all patients had the same follow-up time. The mean time was 4 years.

Appendix D – EAC changes to errors in the company's submitted model

Error 1

In the company's "Calcs for TPs" tab, the cell calculation for 6-monthly probability of discontinuation of steroid treatment is different from the calculations used in all other cells for that tab. This error affected the cost of the stepped pathway. For the 6-monthly probability of discontinuation of steroid treatment 15% is divided by 65 and the reason was not clear. The EAC identified two possible solutions possible and both gave the same answer. One was to divide by 100 and not 65. The second was to use the same calculation that was used in all the other cells on the tab. The EAC used the latter approach and this lead to iFuse becoming more cost saving, as more people continue to use steroid injections, which are the most costly option in the stepped pathway.

Error 2

The second error in the model identified by the EAC related to the late revision calculation in the "Calcs" tab of the company's submitted model. This error affected the cost of the open surgery. The company's economic submission states that for each type of surgery there is a 50% chance of success after revision. The "Inputs" page of the company's submitted model also implies this. However, under the "Calcs" tab of the company's submitted model iFuse has a 50% chance of success, but open surgery has 50% of the original surgery success probability, resulting in a 27% probability. The change makes open surgery slightly more effective, and less costly. However, the impact is very low due to the small number of revisions.

Appendix E – Values for inputs and results from EAC's one way sensitivity analysis

Parameter	Inputs		Cost difference results		Source of inputs
	Low	High	Low	High	
iFuse vs. open surgery					
Number of Surgeries in 5 Year : iFuse	70	110	-£3,161.72	-£3,164.58	The EAC used the inputs used by the company.
Number of Training Hours : iFuse	3	5	-£3,164.99	-£3,161.94	The EAC used the inputs used by the company.
Surgical Unit Cost : iFuse	132.89	213.72	-£3,163.65	-£3,160.04	The EAC used the inputs used by the company.
Unit cost pre-assessment visit : All	106.74	220.21	-£3,153.99	-£3,169.23	The EAC used the inputs used by the company.
Unit cost of outpatient visit : All	78.98	159.4	-£3,142.43	-£3,174.82	The EAC used the inputs used by the company.
Unit cost of hospital stay : iFuse	260.59	437.18	-£3,264.57	-£3,116.28	Low and high inputs used by the company were kept but were swapped to match the correct HRG code for a hospital stay for iFuse. The company used a HRG code they identified for open surgery in their model.
Bi-annual probability of revision : iFuse	0.003089723	0.005539468	-£3,254.80	-£3,072.38	The EAC used the inputs used by the company.
Procedure time : Open Surg. - Anterior	104	128	-£3,093.90	-£3,335.86	The EAC used the inputs used by the company.
# follow-up visits in first year : iFuse	3	5	-£3,301.20	-£3,025.73	The EAC used the inputs used by the company.
Procedure time : iFuse - Unilateral	50.9	66.9	-£3,308.27	-£3,022.24	The EAC used the inputs used by the company.

Total Consumables Anterior : Open Surg. - Anterior	976	1464	-£3,019.02	-£3,307.91	The EAC used the inputs used by the company.
# follow-up visits in first year : Open Surg.	3	5	-£3,008.11	-£3,318.82	The EAC used the inputs used by the company.
% Good Response to Treatment : iFuse	0.752875838	0.845124162	-£2,932.12	-£3,394.81	The EAC used the inputs used by the company.
Procedure time : Open Surg. - Posterior	138	188	-£2,911.42	-£3,415.51	The EAC used the inputs used by the company.
Length of Stay : Open Surg. - Anterior	3.3	8	-£2,615.34	-£3,373.04	The low input was obtained from the shortest mean length of stay reported by Ledonio et al. (2014a). The high input was obtained from the longest mean length of stay reported by Nystrom et al. (2017).
Total Consumables Posterior : Open Surg. - Posterior	2640	3960	-£2,772.75	-£3,554.18	The EAC used the inputs used by the company.
% Good Response to Treatment : Open Surg.	0.394445528	0.565554472	-£3,564.78	-£2,762.15	The EAC used the inputs used by the company.
Unit cost of hospital stay : Open Surg.	201.63	337.79	-£2,715.69	-£3,578.18	Low and high inputs used by the company were kept but were swapped to match the correct HRG code for a hospital stay for iFuse. The company used a HRG code they identified for open surgery in their model.
Length of Stay : Open Surg. - Posterior	1	7	-£2,679.83	-£3,647.10	The low and high inputs were obtained from the shortest and longest length of stay reported in a range by Khurana et al. (2009).
Total Consumables : iFuse	3247.2	4870.8	-£4,015.63	-£2,311.30	The EAC used the inputs used by the company.

Unit cost of theatre time : All	6.3872	27.6728	-£2,096.90	-£4,230.02	The EAC used the inputs used by the company.
% Anterior/posterior : Open Surg.	0	1	-£4,484.80	-£1,842.13	The EAC used the inputs used by the company.
Total Pain Management : All	58.38	831.99	-£1,802.60	-£4,524.33	The low and high inputs were calculations used by the company in their original model. The low cost is based on a low medication cost and a unit cost of a GP visit. The high cost is based on a high medication cost, unit cost of a GP visit and a unit cost of an outpatient visit. The EAC obtained new costs for low and high medication.
Length of Stay : iFuse - Unilateral	0	7	-£3,483.41	-£683.87	The low and high inputs were obtained from the shortest and longest length of stay reported in a range by Duhon et al. (2016).
Bi-annual probability of revision : Open Surg.	0.00085	0.05406	-£2,054.33	-£5,806.28	The EAC used the inputs used by the company.
iFuse vs. stepped pathway					
Number of Surgeries in 5 Year : iFuse	70	110	£558.97	£556.11	The EAC used the inputs used by the company.
Number of Training Hours : iFuse	3	5	£555.69	£558.75	The EAC used the inputs used by the company.
Surgical Unit Cost : iFuse	132.89	213.72	£557.04	£560.64	The EAC used the inputs used by the company.
RF Ablat. to No Treat : Stepped	0.1	0.5	£577.21	£547.66	The EAC used the inputs used by the company.
Procedure Costs : RF Ablat.	511.635	995.5642	£577.74	£539.84	The EAC used the inputs used by the company.

% Good Response to Treatment : Revision	0.19975	0.59925	£588.92	£546.74	The EAC used the inputs used by the company.
# Procedures in 6 months : RF Ablat.	0.25	0.5	£557.22	£496.62	The EAC used the inputs used by the company.
% Good Response to Treatment : RF Ablat.	0	0.5	£529.41	£598.94	The EAC used the inputs used by the company.
Unit cost pre-assessment visit : All	106.74	220.21	£483.18	£602.29	The EAC used the inputs used by the company.
Unit cost of hospital stay : iFuse	260.59	437.18	£456.11	£604.41	Low and high inputs used by the company were kept but were swapped to match the correct HRG code for a hospital stay for iFuse. The company used a HRG code they identified for open surgery in their model.
Bi-annual probability of revision : iFuse	0.00309	0.005539	£465.88	£648.30	The EAC used the inputs used by the company.
Unit cost of outpatient visit : All	78.98	159.4	£392.74	£645.99	The EAC used the inputs used by the company.
# follow-up visits in first year : iFuse	3	5	£419.48	£694.95	The EAC used the inputs used by the company.
Procedure time : iFuse - Unilateral	50.9	66.9	£412.42	£698.45	The EAC used the inputs used by the company.
% Good Response to Treatment : iFuse	0.752876	0.845124	£788.57	£325.87	The EAC used the inputs used by the company.
Steroid Inj. to No Treat : Stepped	0	0.2	£303.70	£932.91	The EAC used the inputs used by the company.
Steroid Inj. to RF Ablat. : Stepped	0	0.2	£95.51	£998.51	The EAC used the inputs used by the company.
Procedure Costs : Steroid Inj.	400	600	£1165.87	-£51.43	The EAC's cost for a steroid injection was varied by ±20%.

Unit cost of theatre time : All	6.3872	27.6728	-£101.93	£1216.37	The EAC used the inputs used by the company.
% Good Response to Treatment : Steroid Inj.	0.2	1	£1069.10	-£295.91	The EAC used the inputs used by the company.
Length of Stay : iFuse - Unilateral	0	7	£237.27	£3036.82	The low and high inputs were obtained from the shortest and longest length of stay reported in a range by Duhon et al. (2016).
# Procedures in 6 months : Steroid Inj.	1	3	£1571.63	-£2486.01	The EAC used the inputs used by the company.
Total Pain Management : All	58.38	831.99	£2798.77	-£1684.33	The low and high inputs were calculations used by the company in their original model. The low cost is based on a low medication cost and a unit cost of a GP visit. The high cost is based on a high medication cost, unit cost of a GP visit and a unit cost of an outpatient visit. The EAC obtained new costs for low and high medication.