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Randomized Controlled Trial of Minimally Invasive Sacroiliac Joint Fusion Using Triangular Titanium Implants Vs Nonsurgical Management for Sacroiliac Joint Dysfunction: 12-Month Outcomes

BACKGROUND: Sacroiliac joint (SIJ) dysfunction is a prevalent cause of chronic, unremitting lower back pain.

OBJECTIVE: To concurrently compare outcomes after surgical and nonsurgical treatment for chronic SIJ dysfunction.

METHODS: A total of 148 subjects with SIJ dysfunction were randomly assigned to minimally invasive SIJ fusion with triangular titanium implants (n = 102) or nonsurgical management (n = 46). Pain, disability, and quality-of-life scores were collected at baseline and at 1, 3, 6, and 12 months. Success rates were compared by the use of bayesian methods. Crossover from nonsurgical to surgical care was allowed after the 6-month study visit was complete.

RESULTS: Six-month success rates were higher in the surgical group (81.4% vs 26.1%; posterior probability of superiority > 0.9999). Clinically important ($\geq$ 15 point) Oswestry Disability Index improvement at 6 months occurred in 72.5% of the SIJ fusion group vs 13% of the nonsurgical management group ($P < .001$). At 12 months, improvements in SIJ pain and Oswestry Disability Index were sustained in the surgical group. Subjects who crossed over had improvements in pain, disability, and quality of life similar to those in the original surgical group. Adverse events were slightly more common in the surgical group (1.3 vs 1.1 events per subject; $P = .31$).

CONCLUSION: This Level 1 study showed that minimally invasive SIJ fusion using triangular titanium implants was more effective than nonsurgical management at 1 year in relieving pain, improving function, and improving quality of life in patients with SIJ dysfunction caused by degenerative sacroiliitis or SIJ disruptions. Pain, disability, and quality of life also improved after crossover from nonsurgical to surgical treatment.

KEY WORDS: Sacroiliac joint dysfunction, Chronic lower back pain, Randomized controlled trial, Minimally invasive surgery

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ABBREVIATIONS: EQ-5D, EuroQoL-5D; **INSITE,** Investigation of Sacroiliac Fusion Treatment; **MCS,** mental component summary; **NSM,** nonsurgical management; **ODI,** Oswestry Disability Index; **PCS,** physical component summary; **RFA,** radiofrequency ablation; **SF-36,** Short Form-36; **SIJ,** sacroiliac joint; **TTO,** time trade-off; **VAS,** visual analog scale

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The sacroiliac joint (SIJ) is responsible for force and energy transfer from the spine to the pelvis. Proper functioning of the SIJ is thought to require a combination of articular congruity and balanced muscular/ligamentous compression (ie, "form and force closure"[1]). Imbalance between these components results in increased stresses and pathological motion, causing altered muscle activation,[2] pain, and disability.

Pain emanating from the SIJ was first described in the early 1900s.[3] The SIJ contains mechanoreceptors[4] and nociceptive receptors.[5] Pressurization

of the SIJ in healthy volunteers can elicit pain.[6] The joint is multiply innervated such that anesthetics applied to the exiting dorsal sacral nerve roots blocks sensation outside the joint but not pain elicited by joint pressurization.[7] In blinded randomized trials, radiofrequency ablation (RFA) of sacral nerve roots was effective in at least temporarily relieving pain in patients with SIJ pain,[8,9] providing definitive proof not only that the SIJ is a source of pain but also that the pain can be treated successfully.

SIJ pathology can cause proximal buttocks pain that may radiate into the lower back, groin, or lower extremity.[6] In a detailed diagnostic study of outpatients with lower back pain, the SIJ was thought to be the source of up to 15% of all chronic lower back pain.[10] SIJ pain is an even more common explanation for post–lumbar fusion lower back pain.[10-12] Causes of SIJ pain include osteoarthritic degeneration, SIJ disruption as a result of trauma or pregnancy, inflammatory disease, tumor, and infection. Radiographic findings in the SIJ are common[13] but are not necessarily predictive of the presence of SIJ pain. In typical practice, cross-sectional imaging of the pelvis and lumbar spine is done to rule out other concomitant pathology that could explain pain in the buttocks or groin.

Nonsurgical treatments for SIJ disorders include medical management, physical therapy, manipulation, intra-articular steroid injections, prolotherapy, chiropractic, and RFA. Other than for RFA, no high-quality evidence exists to support the effectiveness of nonsurgical treatments for SIJ pain. Two blinded controlled trials of RFA of sacral nerve roots have shown short-term improvement in pain[8,9]; a 12-month follow-up study showed a modest long-term response rate after this treatment.[14]

SIJ fusion was first described in the 1920s,[15] and several single-center retrospective reports suggest that it may be moderately effective for the treatment of pain in this patient population.[16-21] Pain relief is likely mediated by SIJ stabilization, reducing the need for active coordinated muscular control and passive ligamentous stability to facilitate effective load transfer across the SIJ. Unfortunately, open SIJ fusion is highly invasive and is associated with long hospital stays and recovery times, high nonunion rates (9%-41%[18,22,23]), poor long-term response rates, and low levels of satisfaction.[24]

Minimally invasive SIJ fusion systems are now available using various US Food and Drug Administration–cleared implants. Placed through less invasive surgical approaches, these devices are designed to provide the benefits of SIJ fusion with faster recovery times as a result of reduced iatrogenic injury to surrounding tissues. Minimally invasive SIJ fusions now account for 90% of all SIJ fusions.[25] Most published reports (primarily single-center retrospective cohorts[26-32] and a combined multicenter analysis[33]) describe the placement of multiple triangular titanium implants coated with a porous titanium plasma spray (iFuse Implant System, SI-BONE, Inc, San Jose, California) across the SIJ under fluoroscopic guidance. These reports provide evidence that minimally invasive SIJ fusion relieves pain and disability.

Previously, we reported 6-month results of a randomized clinical trial comparing SIJ fusion using iFuse Implant System and nonsurgical management (NSM).[34] This study showed that SIJ fusion produced superior improvements in pain, disability, and quality-of-life outcomes at 1, 3, and 6 months after treatment relative to NSM. This report presents the 12-month follow-up from this study, including an analysis of subjects who crossed over from NSM to surgical treatment after the 6-month visit (which was permitted according to the study protocol).

METHODS

Investigation of Sacroiliac Fusion Treatment (INSITE) is an ongoing prospective, multicenter, parallel-group, unblinded randomized controlled trial. Enrollment took place between January 2013 and May 2014 at 19 spine surgery clinics in the United States. The study protocol (registered on http://www.clinicaltrials.gov [NCT01681004]) was approved by the Institutional Review Board at each participating clinical site before patient enrollment. The study was sponsored by the device manufacturer (SI-BONE, Inc). All study sites underwent both remote and periodic on-site data monitoring so that all study data were 100% source verified.

Adult (age, 21-70 years) patients were eligible to participate if they had a confirmed diagnosis of SIJ dysfunction caused by degenerative sacroiliitis or SIJ disruption. Diagnosis was based on typical history (pain in the back below L5, buttocks, or legs, including a positive Fortin finger test[35]), SIJ pain elicited on at least 3 of 5 established physical examination provocative tests (Figure 1),[36] and at least a 50% transient decrease in SIJ pain 30 to 60 minutes after image-guided local anesthetic injection into the SIJ (with arthrogram confirmation) performed within 3 months before screening. Degenerative sacroiliitis was defined in the study as established SIJ-mediated pain in the context of either radiographic evidence of SIJ degeneration (sclerosis, osteophytes, subchondral cysts, or vacuum phenomenon) evident on computed tomography (CT) or x-rays or a history of prior lumbar fusion. SIJ disruption was defined in the study as SIJ-mediated pain in the context of asymmetric widening of SIJs on CT or x-rays or the presence of significant contrast leakage during a diagnostic SIJ block. Eligibility also required a baseline score of at least 30% on the Oswestry Disability Index (ODI) and an SIJ pain score (average SIJ pain in the last week) of at least 50 on a 0- to 100-mm visual analog scale (VAS), where 0 represents no pain and 100 represents the worst imaginable pain.

Patients were excluded if any of the following criteria were met: inability to confirm that the pain is arising from the SIJ, SIJ pain secondary to inflammatory conditions, severe back pain deemed to be due primarily to other causes (lumbar disk degeneration, spinal stenosis, etc), history of recent (<1 year) major trauma to the pelvis, metabolic bone disease (either induced or idiopathic), or any condition that made treatment with the study devices infeasible or interfered with the ability of the subject to participate in physical therapy. Patients involved in litigation, on disability leave, or receiving workers' compensation related to their back or SIJ pain were also excluded. Patients who agreed to enroll signed a study-specific informed consent form.

Before randomization, subjects provided a detailed medical history, underwent a physical examination, and completed several questionnaires: SIJ and lower back pain using the above-described VAS, ODI,[37] EuroQoL-5D (EQ-5D),[38] and Short Form-36 (SF-36).[39] The ODI is a validated 10-question survey for disability resulting from back pain. EQ-5D is a 5-question broad quality-of-life measure that can be combined into a single index and represents the time trade-off (TTO)

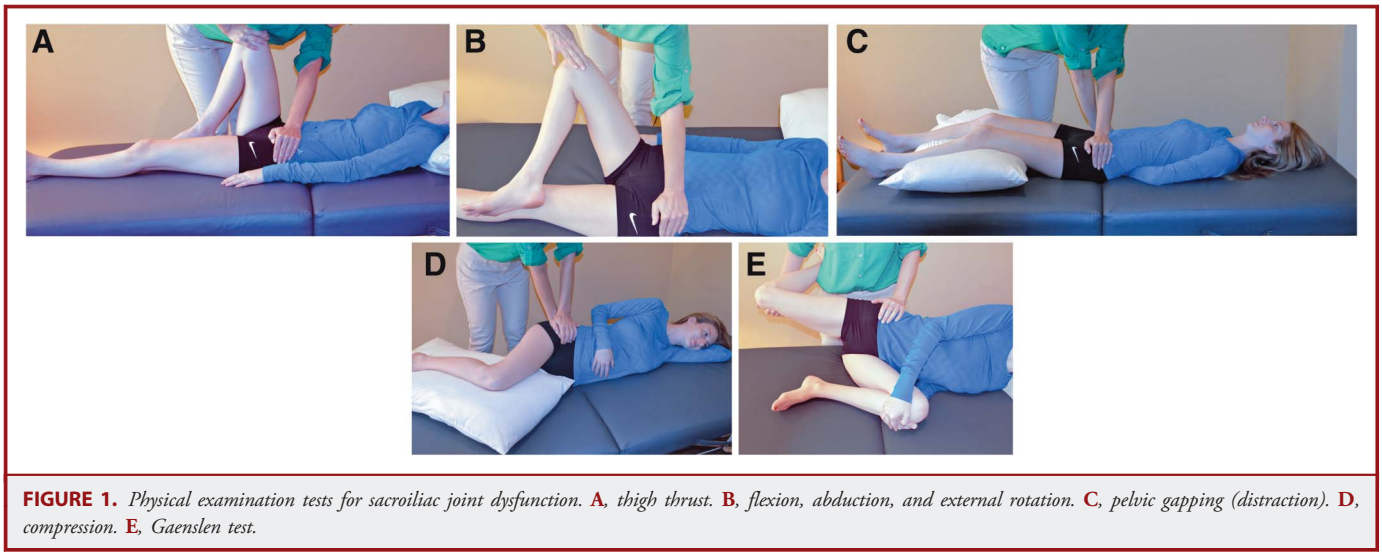

FIGURE 1. *Physical examination tests for sacroiliac joint dysfunction.* **A**, *thigh thrust.* **B**, *flexion, abduction, and external rotation.* **C**, *pelvic gapping (distraction).* **D**, *compression.* **E**, *Gaenslen test.*

utility of current health. EQ-5D also includes a 0- to 100-mm health thermometer, where 0 means death and 100 means perfect health. SF-36 is a 36-question, 8-subscaled generic quality-of-life measure. SF-36 Physical Component Summary (PCS) summarizes overall physical health with population norms with a mean of 50 and standard deviation of 10. Similarly, SF-36 Mental Component Summary (MCS) summarizes overall mental health with equivalent population norms.

Randomization

After baseline assessment, subjects were randomly assigned to either SIJ fusion or NSM. Randomization was stratified by site and underlying diagnosis (degenerative sacroiliitis or SIJ disruption) in a 2:1 ratio with randomly chosen block sizes of 6 or 9. Randomization sequences were computer generated and obtained via a password-protected study Web site. Subjects were not blinded to treatment.

Interventions

NSM was consistent with existing US practices and consisted of anti-inflammatory and pain medications as directed by the site investigator, physical therapy following American Physical Therapy Association guidelines,[40] intra-articular SIJ steroid injections, and RFA of sacral nerve roots, all of which were delivered in a stepwise fashion as needed to address pain and disability and tailored to each individual patient's needs. No cognitive behavioral therapy for SIJ pain treatment was used because no published data support the effectiveness of this method for SIJ pain and because cognitive behavioral therapy is not a well-accepted modality in the modern US healthcare system.

Minimally invasive SIJ fusion was performed as described previously[34] within 30 days of baseline assessment. All procedures were performed under general anesthesia with fluoroscopy or 3-dimensional computer navigation based on intraoperative CT (O-arm) imaging. The procedure involves placement of implants (see below) across the SIJ through a lateral incision with the goal of immediate transarticular stabilization. The porous coating of the device promotes long-term biological fixation and fusion of the SIJ. Subjects were discharged home at the surgeon's discretion. Before discharge, subjects were re-evaluated for the occurrence of adverse events. Postoperatively, subjects were asked to remain at heel-toe touch-down weight bearing using a front-wheeled walker or crutches for 3 weeks, which was progressively increased until the subjects were fully ambulatory. Subjects were asked to undergo individualized physical therapy twice a week for 6 weeks starting 1 to 3 weeks after surgery.

Device Description

The iFuse Implant System is a US Food and Drug Administration–cleared (K080398) triangular titanium implant that is coated with a porous titanium plasma spray. The triangular shape allows an interference fit that provides immediate stabilization and minimizes micromotion and rotation of the instrumented SIJ. The porous plasma spray coating allows biological fixation of bone, a concept that is commonly used by several orthopedic devices such as hip, knee, and shoulder implants. The iFuse implant is available in configurations ranging from 30 to 70 mm in length and either 4 or 7 mm in inscribed diameter. The manufacturer recommends placement of at least 2 implants across the SIJ.

Crossover

Subjects assigned to NSM were permitted to cross over to surgical treatment at any time after the 6-month visit was completed. Study investigators required the trial to have a crossover component because patients with SIJ dysfunction have markedly reduced quality of life,[41] because limited evidence was available to support the effectiveness of NSM for this condition, and because preliminary results from SIJ fusion using the study device were very promising. Investigators believed that precluding crossover would have unnecessarily prolonged enrollment and resulted in a nongeneralizable population. Because the study device was already commercially available, patients could have simply elected to obtain SIJ fusion outside the study rather than participating in the study. However, no subjects crossed over early.

Follow-up

All subjects were evaluated at follow-up visits scheduled at 1, 3, 6, and 12 months after assignment to NSM or SIJ fusion surgery. Follow-up

visits continue to 24 months. These assessments consisted of an overall health assessment interview; documentation of ambulatory status, work status, and medication use for pain; and physical examination findings. At each visit, patients completed quality-of-life questionnaires. The primary radiographic end point of the study is based on a CT scan of the pelvis obtained at 24 months; this outcome is pending and will be reported separately.

Adverse events, defined according to an international clinical trial standard (ISO14155:2011), were monitored continuously and recorded at all study visits. For each event, investigators were asked to rate severity and relationship to the study device or NSM treatment, the surgical procedure, and, if present, pre-existing conditions. Relatedness was captured as definitely, probably, possibly, or unlikely related or unrelated to the device, procedure, or pre-existing condition. All adverse events were grouped by body system.

Cohorts, Study End Points, and Statistical Analysis

The primary analysis cohort consists of subjects who were enrolled (ie, were eligible and consented) and underwent the assigned study treatment. The primary study end point, evaluated at 6 months after the most recent SIJ fusion (to accommodate subjects with planned staged bilateral surgery), was a binary success/failure composite end point. A subject was considered a success if all of the following were met: reduction from baseline VAS SIJ pain by at least 20 mm, absence of device-related serious adverse events, absence of neurological worsening related to the lumbosacral nerve roots, and absence of surgical reintervention (removal, revision, reoperation, or supplemental fixation) for SIJ pain. The 20-mm threshold was selected as the minimum clinically important difference in chronic lower back pain.[42,43] An intent-to-treat approach was used for the primary end point, in which missing values for the primary end point were assumed to be failures. According to the protocol, subjects who crossed over were deemed to be NSM failures for the patient success end point.

A bayesian analysis was used such that study success was declared if the posterior probability that the success rate in the SIJ fusion group exceeded that of the control group was at least 0.975. A noninformative Jeffreys[44] prior distribution was used. The 0.975 probability threshold is akin to a 1-sided frequentist α value of 0.025. The maximum study sample size of 150 subjects was determined via extensive pretrial simulations (performed by Berry Consultants LLC) to have >80% power under baseline assumptions about success rates (70% for SIJ fusion vs 30% for NSM). Power calculations assumed no early crossover (none occurred). Full study enrollment was achieved before the first preplanned interim analysis could be done. Prespecified subgroup analyses included underlying diagnosis (degenerative sacroiliitis vs SIJ disruption), history of prior lumbar fusion, smokers vs nonsmokers, and unilateral vs bilateral SIJ pain.

The secondary effectiveness end points of the study included improvement from baseline in VAS, ODI, SF-36 PCS, and EQ-5D scores and treatment satisfaction. Changes from baseline were compared by the use of unpaired *t* tests or repeated-measures analysis of variance and a standard frequentist statistical approach. In subjects who crossed over, improvements were calculated with the use of both baseline and 6-month precrossover values as the new baseline.

Analyzing improvements in secondary end points after crossover from NSM to surgery to the originally assigned NSM treatment would result in severe bias for any comparisons after month 6 given that these scores in the NSM group showed only modest improvement (see Results). Rather, separate analyses were performed for subjects who chose to cross over vs those who did not. In addition, we calculated threshold analyses (ie, the proportion of subjects achieving a given threshold improvement) in which the improvement resulted from the initially assigned treatment only. Thus, this approach equates crossover with failure.

The number of adverse events per subject was compared by the use of Poisson regression. Adverse event rates are presented during the first 6 months (before crossover, unbiased comparison) and during the first 12 months (during which crossover limits the comparison). The change in the proportion of subjects using opioids was calculated with a conditional relative odds ratio.[45] Confidence intervals for proportions were calculated with standard methods. All statistical analyses were performed with R.[46] The study manuscript was written jointly by study authors and the study sponsor. The study sponsor performed statistical analysis.

RESULTS

Of the 442 subjects at 19 sites who were screened for participation, 159 (37.8%) were enrolled. Eleven subjects withdrew before treatment (1 before randomization and 10 after randomization but before any treatment was performed), yielding a total of 148 enrolled, randomized (102 to SIJ fusion and 46 to NSM), and treated subjects. Enrollment took place from January 2013 to May 2014.

Baseline Characteristics

Patient characteristics are listed in Table 1. Subject characteristics were similar across assignment groups. The mean subject age was 51.3 years; 12.2% (18 subjects) were ≥65 years of age. The majority (94.6%) of subjects were white, and 103 (69.6%) were women. Subjects were highly debilitated by SIJ pain, as indicated by high baseline pain ratings (mean, 82.3 on the 0-100 scale) and ODI scores (mean, 56.8). Nineteen percent were not working because of chronic pain. The duration of pain before enrollment averaged 6.4 years (range, 0.5-40.7 years); 87.2% had pain for ≥1 year, and 73.6% had pain for ≥2 years. Pain locations reported by subjects were largely centered over the posterior superior iliac spine, but distant pain or pain radiating anteriorly or posteriorly was also frequently reported. A large proportion of subjects (38.5%) had undergone prior lumbar fusion; 14.9% had been diagnosed with lumbar stenosis; 10.8% had concomitant hip disorders; and 7.4% had sustained previous sacral trauma. The majority of trial subjects had previously undergone SIJ-specific physical therapy (72.3% of subjects) and SIJ steroid injections (85.8%); 16.2% had undergone prior RFA of the sacral nerve roots. Two-thirds (66.2%) were taking opioid pain medications at baseline, and every subject reported that multiple activities commonly caused or worsened the SIJ pain. Quality of life was substantially diminished, as indicated by low EQ-5D TTO scores (mean, 0.45) and low SF-36 scores (mean PCS, 30.4; mean MCS, 43.1), confirming that SIJ dysfunction brings about significant burden of disease.[41]

Subject Trial Flow

Ten subjects withdrew before receiving any treatment (3 assigned to NSM, 7 assigned to SIJ fusion), leaving 148 randomized subjects who received study treatment. Six-month follow-up was obtained in 101 of 102 subjects (99%) treated with

TABLE 1. Characteristics of Enrolled Subjects[a]

Characteristic	NSM (n = 46)	SIJ Fusion (n = 102)	*P* Value[b]
Age, mean (SD, range), y	53.8 (10.6, 29.5-71.1)	50.2 (11.4, 25.6-71.7)	.07
≥65 y old, n (%)	8 (17.4)	10 (9.8)	
Female, n (%)	28 (60.9)	75 (73.5)	.13
Race, n (%)			.68
White	43 (93.5)	97 (95.1)	
Black	2 (4.3)	3 (2.9)	
American Indian	0 (0)	1 (1.0)	
Other	1 (2.2)	1 (1.0)	
Ethnicity, n (%)			.26
Hispanic or Latino	4 (8.7)	4 (3.9)	
Body mass index, mean (SD, range), kg/m^2	30.6 (6.6, 19.4-48.9)	30.3 (6.4, 14.1-49.5)	.80
Smoking status, n (%)			.01
Current smoker	3 (6.5)	26 (25.5)	
Former smoker	13 (28.3)	30 (29.4)	
Never smoker	30 (65.2)	46 (45.1)	
Ambulatory without assistance, n (%)	41 (89.1)	89 (87.3)	>.99
Work status, n (%)			.99
Working full-time	21 (45.7)	45 (44.1)	
Working part-time	4 (8.7)	9 (8.8)	
Not working, student	0 (0)	1 (1.0)	
Not working, retired	9 (19.6)	21 (20.6)	
Not working owing to back pain	8 (17.4)	20 (19.6)	
Not working, other reason	4 (8.7)	6 (5.9)	
Prior lumbar fusion, n (%)	17 (37.0)	40 (39.2)	.86
Underlying diagnosis, n (%)			>.99
Degenerative sacroiliitis	40 (87.0)	88 (86.3)	
Sacroiliac joint disruption	6 (13.0)	14 (13.7)	
Years of pain, mean (range)	5.0 (0.5-38.9)	7.0 (0.5-40.7)	.13
Pain syndrome, n (%)			
Pain began peripartum	4 (8.7)	8 (7.8)	.23
Pain radiates down leg	41 (89.1)	89 (87.3)	>.99
Groin pain	29 (63.0)	60 (58.8)	.72
Pain worse with sitting	41 (89.1)	89 (87.3)	>.99
Pain worse with rising	41 (89.1)	88 (86.3)	.79
Pain worse with walking	42 (91.3)	87 (85.3)	.43
Pain worse with climbing stairs	41 (89.1)	93 (91.2)	.76
Pain worse descending stairs	37 (80.4)	82 (80.4)	>.99
Prior treatments, n (%)			
Physical therapy	36 (78.3)	71 (69.6)	.32
Steroid SIJ injection	42 (91.3)	85 (83.3)	.31
RFA	4 (8.7)	20 (19.6)	.14
Taking opioids, n (%)	29 (63.0)	69 (67.6)	.58
Proportion with lumbar stenosis, n (%)	7 (15.2)	15 (14.7)	.82
Proportion with hip diagnosis, n (%)	2 (4.3)	14 (13.7)	.15
Proportion with sacral trauma, n (%)	3 (6.5)	8 (7.8)	>.99
VAS SIJ pain score, mean (±SD)	82.2 (9.9)	82.3 (11.9)	.93
ODI score, mean (±SD)	56.0 (14.0)	57.2 (12.8)	.63
SF-36, mean (±SD)			
PCS	30.8 (6.1)	30.2 (6.2)	.57
MCS	43.3 (12.1)	43.0 (11.5)	.86
EQ-5D			
TTO index	0.47 (0.19)	0.44 (0.18)	.34
Health thermometer	57.8 (22.9)	53.2 (23.8)	.28

[a]EQ-5D, EuroQoL-5D; MCS, mental component summary; NSM, nonsurgical management; ODI, Oswestry Disability Index; PCS, physical component summary; RFA, radiofrequency ablation; SF-36, Short Form-36; SIJ, sacroiliac joint; TTO, time trade-off; VAS, visual analog scale.
[b]Fisher *P* value for ordinal variables; *t* test for continuous variables.

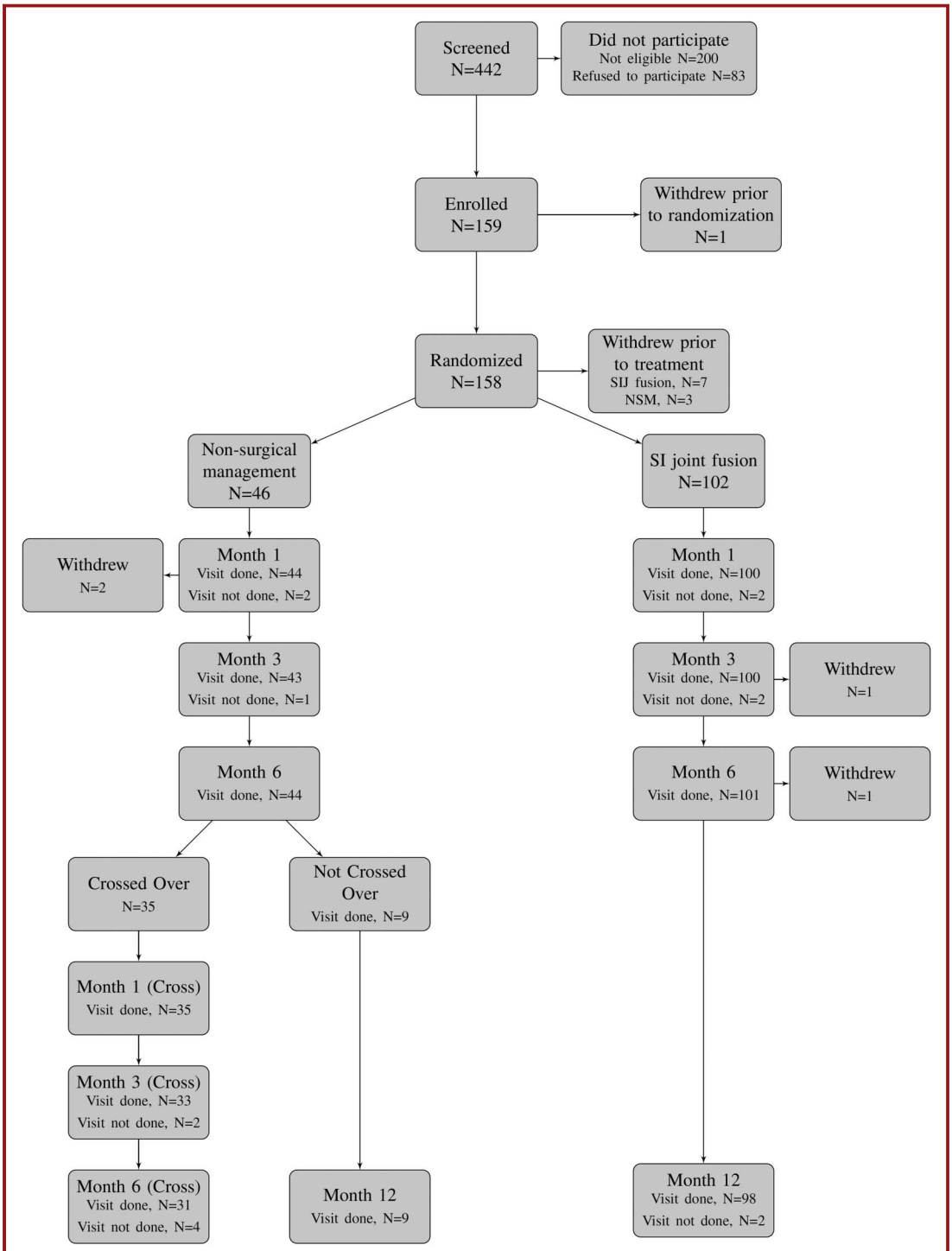

FIGURE 2. *Subject flow through the study, including crossover visits.*

SIJ fusion and 44 of 46 subjects (95.7%) treated with NSM. Twelve-month follow-up was obtained in 98 of 102 SIJ fusion subjects (96%) and 40 of 46 NSM subjects (87.0%; Figure 2). In the SIJ fusion group, 3 subjects withdrew from the study before month 6, and an additional 1 subject withdrew after month 6.

Procedure Characteristics

One hundred two subjects underwent SIJ fusion (76 unilateral, 26 planned bilateral). For the index procedure, the mean procedure time was 45 minutes (range, 14-140 minutes; Table 2). The mean fluoroscopy time was 2.5 minutes (range, 0.13-25 minutes), and the mean estimated blood loss was 33 cm^3 (all subjects had blood loss $\leq$100 cm^3 except 1 subject with a body mass index of 48 kg/m^2 who had 250-cm^3 blood loss); no patient required a transfusion. Three implants were used in most cases (91.2%), and nearly all implants (99.3%) were 7 mm in diameter. Median hospital length of stay was 1 day (range, 0-7 days). Three prolonged hospital stays ($\geq$3 days; 2.9%) were related to patient comorbidities and not to device- or procedure-related adverse events.

Nonsurgical Management

Of the 46 subjects assigned to NSM, all but 1 received physical therapy during the 6 months after treatment assignment. During the first 6 months after assignment to NSM, 34 subjects (73.9%) underwent at least 1 steroid injection (6 subjects underwent 2 injections), and 21 (45.7%) underwent RFA of the sacral nerve roots. Forty NSM subjects (87.0%) underwent at least 2 types of NSM treatments in addition to pain medications.

TABLE 2. Minimally Invasive Sacroiliac Joint Fusion Procedure Characteristics (n = 102)[a]

Characteristic	Value
Target joint, n (%)	
Right	55 (53.9)
Left	47 (46.1)
Procedure time, min, n (%)	
Mean (SD, range)	44.9 (22.3, 14-140)
<30	30 (29.4)
30-60	50 (49.0)
>60	22 (21.6)
Fluoroscopy time, n (%)	
Mean (SD, range), min	2.5 (3.6, 0.13-25)
0-1 min	17 (16.7)
1-2 min	51 (50.0)
2-5 min	21 (20.6)
>5 min	7 (6.9)
Estimated blood loss, n (%)	
Mean (SD, range), cm^3	32.7 (32.8, 0.5-250)
0-50 cm^3	92 (90.2)
50-100 cm^3	9 (8.8)
>100 cm^3	1 (1.0)
Implants used, n (%)	
2	5 (4.9)
3	93 (91.2)
4	4 (3.9)
Hospital length of stay, n (%)	
Mean (SD, range), d	0.78 (0.97, 0-7)
Discharged same day	42 (41.2)
1-2 d	57 (55.9)
≥3	3 (2.9)

[a]Only the index side procedure is reported.

Crossover

No protocol-defined early crossover occurred. As of June 2015, 35 of 44 NSM subjects (79.5%) who were still participating had crossed over to surgical treatment. All crossovers underwent SIJ fusion with the study device, and all crossovers were after the month 6 visit.

Primary End Point

By month 6, 83 of 102 SIJ fusion subjects (81.4%; 95% posterior credible interval, 72.4-88.4) and 12 of 46 NSM subjects (26.1%; 95% posterior credible interval, 14.3-41.1) met the primary success end point of the study. In the SIJ fusion group, 1 subject was a failure for the 6-month primary end point owing to both inadequate pain reduction and immediate revision required for symptomatic implant malposition. No subject assigned to NSM was classified as failure for reasons other than inadequate pain reduction. The intent-to-treat difference in success rates was 54.5% (95% posterior credible interval, 39.1-68.2), representing a >3-fold difference in success rate, and the posterior probability that the success rate was higher in the SIJ fusion group was >0.9999. Prespecified subgroup analysis (Table 3) showed similar differences in success rates across treatments by underlying diagnosis, history of prior lumbar fusion, smoking status, or unilateral vs bilateral SIJ pain.

Secondary End Points

In the SIJ fusion group, mean SIJ pain improved from 82.3 at baseline to 30.4 at the 6-month follow-up (52.0-point improvement; $P < .001$) and 28.3 at the 12-month follow-up (54.2-point improvement; $P < .001$; Figure 3 and **Table**, **Supplemental Digital Content 1**, http://links.lww.com/NEU/A770). In the NSM group, mean SIJ pain improved from 82.2 at baseline to 70.3 at 6 months (mean improvement, 12.2 points; $P = .001$). The improvement in SIJ pain after SIJ fusion exceeded that of NSM by a mean of 38.2 points ($P < .001$, repeated-measures analysis of variance). Similarly, in the SIJ fusion group, mean ODI decreased from 57.2 at baseline to 29.9 at month 6 and 28.1 at month 12 (improvement, 27.4 and 29.4 points, respectively; $P < .001$; Figure 4). In the NSM group, mean ODI decreased from 56.0 at baseline to 51.6 at 6 months (a 4.6-point improvement; $P = .06$).

According to the study protocol, NSM subjects were allowed to cross over to surgical treatment after the month 6 visit. The protocol asked that at least 2 interventions (physical therapy, SIJ steroid injection, or RFA) be provided to NSM subjects before crossover; 40 of those subjects (87%) were in compliance with this aspect of the protocol. Of the 44 NSM subjects still participating at 6 months, 35 (79.5%) crossed over and 9 (20%) did not. Mean 6-month pain and ODI scores were higher in those who crossed over

TABLE 3. Six-Month Success Rates and Subgroup Analysis[a]

Subgroup	Level	SIJ Fusion, n/N (%)	NSM, n/N (%)	Rate Difference (95% Posterior Credible Interval)[b]
Diagnosis	DS	70/88 (79.5 to 69.6-87.4)	11/40 (27.5 to 14.6-43.9)	51.2 (34.3 to 66.1)
	SD	13/14 (92.9, 66.1 to 99.8)	1/6 (16.7, 0.4 to 64.1)	68.6 (31.0 to 93.1)
History of lumbar fusion	Yes	33/40 (82.5, 67.2 to 92.7)	3/17 (17.6, 3.8 to 43.4)	62.3 (38.6 to 80.8)
	No	50/62 (80.6, 68.6 to 89.6)	9/29 (31.0, 15.3 to 50.8)	48.5 (28.5 to 66.4)
Smoking	Current	20/26 (76.9, 56.4 to 91.0)	1/3 (33.3, 0.8 to 90.6)	38.4 (−9.1 to 76.7)
	Never	39/46 (84.8, 71.1 to 93.7)	7/30 (23.3, 9.9 to 42.3)	59.9 (40.4 to 76.3)
	Former	24/30 (80.0, 61.4 to 92.3)	4/13 (30.8, 9.1 to 61.4)	46.9 (17.5 to 71.9)
Bilateral pain	Yes	26/34 (76.5, 58.8 to 89.3)	2/12 (16.7, 2.1 to 48.4)	56.5 (28.5-77.9)
	No	57/68 (83.8, 72.9 to 91.6)	10/34 (29.4, 15.1 to 47.5)	53.3 (35.1-69.6)
All		83/102 (81.4, 72.4 to 88.4)	12/46 (26.1, 14.3 to 41.1)	54.5 (39.1-68.2)

[a]NSM, nonsurgical management; SIJ, sacroiliac joint.
[b]Point estimate (95% posterior credible interval).

vs those who did not cross over (VAS, 79.0 vs 37.4, a 41.7-point difference, $P = .005$; ODI, 56.1 vs 34.1, a 22.1-point difference, $P = .001$; Table 4). NSM subjects who crossed over had clinically unimportant mean decreases in VAS SIJ pain (5.3 points; $P = .04$) and ODI (2.1 points; $P = .40$) as a result of their NSM treatment before crossover. The proportion of NSM subjects who had at least a 20-point improvement in VAS SIJ pain was lower in those who crossed over (7 of 35, 20%) vs those who did not cross over (5 of 9, 55.6%; $P = .09$). Looking backward, baseline scores in subjects who eventually crossed over were somewhat higher than in those who did not cross over, but the differences were modest (VAS SIJ pain, 83.9 vs 76.5, a 4.9-point difference, $P = .10$; ODI, 58.3 vs 48.9, a 9.4-point difference, $P = .05$).

All crossover subjects underwent minimally invasive SIJ fusion using the study device. Subjects who crossed over had marked improvements in pain and ODI 6 months after crossover surgery:

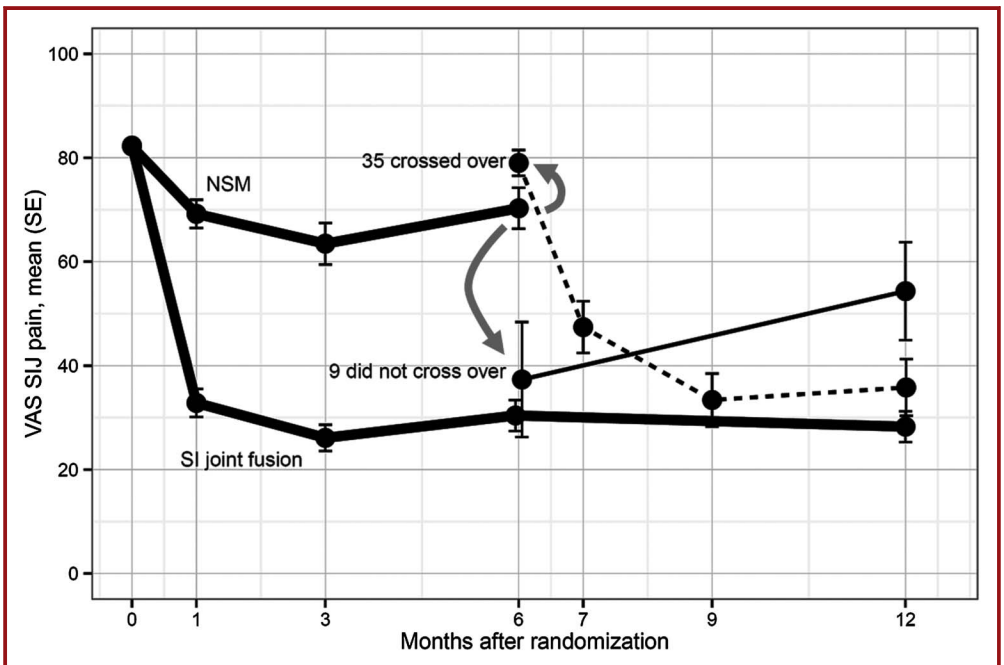

FIGURE 3. *Change in sacroiliac (SI) joint pain by visit. Dark thick lines show those assigned to nonsurgical management (NSM) or SI joint fusion. Dotted line indicates NSM subjects who crossed over to surgery. Thin solid line indicates those who did not cross over to surgery. VAS, visual analog scale.*

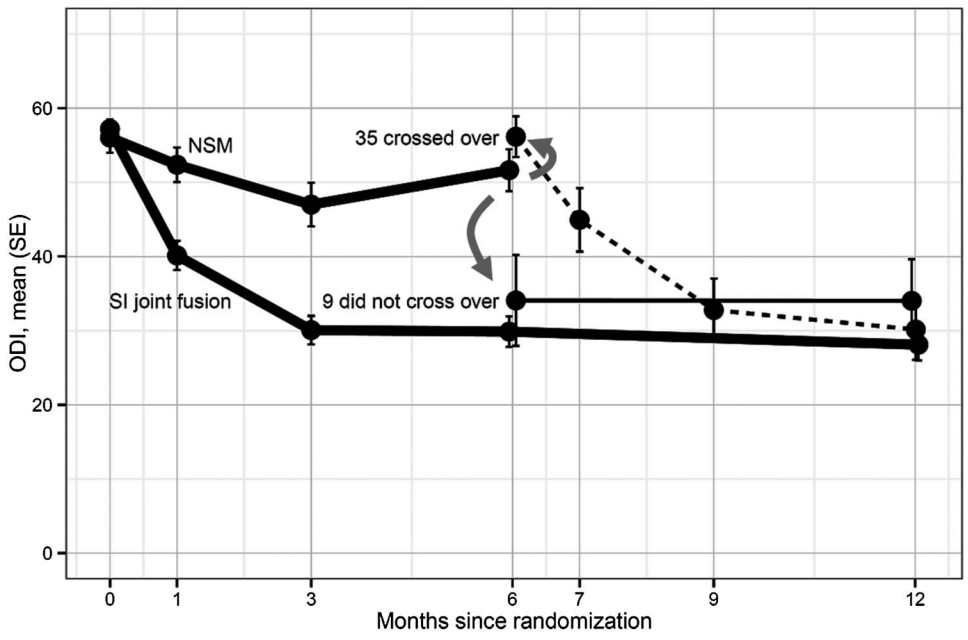

FIGURE 4. *Change in Oswestry Disability Index (ODI) by visit. Dark thick lines show those assigned to nonsurgical management (NSM) or sacroiliac (SI) joint fusion. Dotted line indicates NSM subjects who crossed over to surgery. Thin solid line indicates those who did not cross over to surgery.*

Mean pain ratings went from 79.0 at crossover to 35.8 at 6 months postoperatively (a 42.4-point decrease compared with before crossover; $P < .001$); similarly, mean ODI went from 56.1 at crossover to 30.2 at 6 months postoperatively (a 28.9-point decrease; $P < .001$). Subjects who did not cross over had modest changes from month 6 to 12 (mean worsening of VAS SIJ pain of 17 points; $P = .05$; mean improvement in ODI of 0.5 points; $P = .98$). Improvements in the NSM group subjects 6 months after crossover were almost as high as the 6-month changes in those initially assigned to surgery (drop in VAS SIJ pain, 42.5 vs 52.0 points, respectively; $P = .12$; drop in ODI, 26.3 vs 27.4 points, respectively; $P = .80$).

Table 5 shows the proportion of subjects who had improvements from baseline of at least 20 points in VAS SIJ pain or at least 15 points in ODI scores as a result of the assigned treatment only. By month 12, 81.5% and 72.4% of SIJ fusion subjects met these success criteria; in contrast, in the NSM group, only 12.5% and 10.0% of subjects met these success criteria.

Quality of life was measured with 2 generic assessments, EQ-5D and SF-36. At 6 months, EQ-5D improved by 0.29 points ($P < .001$) in the SIJ fusion group but only 0.06 points ($P = .17$) in the NSM group ($P < .001$ for difference in improvement; Table 6). For subjects who crossed over at 6 months, the 6-month change from baseline was small (0.02 points; $P = .66$), indicating little improvement from baseline before crossover. In contrast, in subjects who did not cross over, EQ-5D TTO improved by 0.20 points ($P = .009$) by month 6. After crossover, EQ-5D TTO improved from 0.47 at month 6 to 0.73 at month 12 (a 0.26-point increase from month 6 [$P < .001$] and a 0.29-point increase from baseline [$P < .001$]). In contrast, there was little change in EQ-5D TTO from month 6 to 12 in those who did not cross over (improvement of <0.01 points; $P = .88$), but the month 12 score for this group was still better than at baseline (improvement of 0.20 points; $P = .008$).

The 6-month changes for SF-36 showed similar findings (Figure 5). Consistent with the physical nature of the illness, baseline physical domain scores were lower than mental domain scores. In the fusion group, mean 6-month changes (y axis) were statistically significant ($P < .001$) for all subdomains and summary scores. In the nonsurgical group, mean 6-month changes were small, and none were statistically significant (all $P > .05$). All 6-month change scores were larger in the fusion group compared with the NSM group (all $P < .05$). Change differences were somewhat larger for physical domain scores vs mental domain scores. Subjects assigned to NSM who crossed over had little improvement in PCS and MCS at 6 months after study initiation (0.2 and 0.6 points). In contrast, 6 months after crossover, these subjects had improvements in PCS and MCS (11.9 and 7.8 points) that were nearly the same as the 6- and 12-month improvements in those originally assigned to SIJ fusion (12.5 and 6.1 points). Subjects who crossed over to surgery had larger improvements in PCS and MCS compared with those who did not cross over.

Six-month satisfaction rates were higher in the surgery group compared with the NSM group (77.2% vs 27.3% very satisfied;

TABLE 4. Comparison of Those Who Crossed Over at Month 6 Vs Those Who Did Not[a]

Characteristic	Crossed Over (n = 35)[b]	Not Crossed or Withdrew (n = 11)	*P* Value[c]
Age, y	53.0 (11.5)	56.5 (6.8)	.34
Female, n (%)	20 (57)	8 (73)	.49
Body mass index, kg/m^2	31.2 (6.5)	28.7 (7.0)	.29
Years of SIJ pain	5.2 (6.9)	4.2 (11.0)	.64
VAS SIJ pain			
Baseline	84.3	76.2	.05
Month 6	79.8	38.7	.003
Change, baseline to month 6	−4.8 (*P* = .06)	−36.8 (*P* = .003)	.007
6 mo after crossover or month 12[d]	37.9	56.5	.17
Change, crossover to 6 mo later	−40.1 (*P* < .001)	+16.3 (*P* = .06)	<.001
ODI			
Baseline	63.9	53.3	.03
Month 6	62.0	37.2	.002
Change, baseline to month 6	−1.9 (*P* = .49)	−15.5 (*P* = .005)	.01
6 mo after crossover or month 12[d]	32.5	36.5	.64
Change, crossover to 6 mo later	−26.8 (*P* < .001)	−0.5 (*P* = .84)	<.001
Underwent during first 6 mo, %			
Physical therapy	35/35 (100)	10/11 (90.9)	.24
At least 1 SIJ injection	27/35 (77.1)	7/11 (63.6)	.44
At least 1 RFA	15/35 (42.9)	6/11 (54.5)	.73

[a]ODI, Oswestry Disability Index; RFA, radiofrequency ablation; SIJ, sacroiliac joint; VAS, visual analog scale.
[b]*P* values compare within-group changes.
[c]*P* values compare those who crossed over and those who did not cross over.
[d]That is, month 12 after initiation of nonsurgical management.

P < .001); specifically, 79.2% of surgery subjects said they would definitely have the procedure again. At 12 months, the surgery satisfaction rate was still high (77.6% very satisfied, 93.9% very or somewhat satisfied). Satisfaction was high among NSM subjects who crossed over (22 of 31, 71.0%, very satisfied 6 months after surgery). In those assigned to SIJ fusion, 80 (79.2%) and 73 (74.5%) reported at 6 and 12 months, respectively, that they would definitely have the surgery again.

At baseline, 67.6% and 63% of SIJ fusion and NSM subjects were taking ≥1 opioid analgesics for SIJ or lower back pain. By month 6, the proportions were 58.4% and 70.5%, representing a 9% decrease in use for the fusion group and a 7.5% increase in the NSM group (*P* = .08). At 12 months, 52% of participating subjects in the surgical group were taking opioid analgesics (*P* = .01 for change from baseline), and 55% of NSM subjects were taking opioids (*P* = .61 for change).

Adverse Events

Adverse events were defined per an international clinical trial standard as any negative change in health. In the first 180 days after SIJ fusion or the beginning of NSM, 178 adverse events were reported (129 in the surgery group and 49 in the NSM group; Table 7). The mean number of events per subject was slightly

TABLE 5. Improvement in Visual Analog Scale Sacroiliac Joint and Oswestry Disability Index Attributable to the Assigned Treatment Over Time[a]

	VAS SIJ Pain Improvement by at Least 20 Points, t/n (%)[b]		ODI Improvement by at Least 15 Points, t/n (%)[b]	
Months	iFuse	NSM	iFuse	NSM
1	85/100 (85.0)	13/45 (28.9)	49/100 (49.0)	6/45 (13.3)
3	87/100 (87.0)	17/44 (38.6)	72/100 (72.0)	13/44 (29.5)
6	83/101 (82.2)	12/44 (27.3)	74/101 (73.3)	6/44 (13.6)
12	80/98 (81.6)	5/40 (12.5)	71/98 (72.4)	4/40 (10.0)

[a]NSM, nonsurgical management; ODI, Oswestry Disability Index; SIJ, sacroiliac joint; VAS, visual analog scale.
[b]Number who had threshold change/number evaluated.

TABLE 6. Quality-of-Life Scores by Treatment and Visit[a]

	Baseline Mean (SD)	Month 6 Mean (SD)	6-mo Change, Mean (SD, *P* Value)[b]	*P* Value Across Groups[c]	Month 12 Mean (SD)	12 Month Change Mean (SD, *P* Value)
SF-36						
PCS						
SIJ fusion (n = 102)	30.2 (6.2)	42.6 (10.1)	12.5 (10.5, <.001)		43.1 (10.3)	13.0 (9.9, <.001)[b]
NSM (n = 46)	30.8 (6.1)	32.1 (7.6)	1.3 (8.2, .30)	<.0001	—	—
Crossed (n = 35)	30.4 (6.4)	30.5 (6.2)	0.2 (7.5, .90)		42.4 (10.6)	11.9 (11.6, <.001)
Did not cross (n = 11)	32.1 (4.9)	38.2 (9.8)	5.7 (9.5, .11)	.07	37.8 (9.5)	5.3 (8.2, .09)
MCS						
SIJ fusion	43.0 (11.5)	49.2 (11.4)	6.1 (11.3, <.001)		50.4 (11.0)	7.2 (12.4, <.001)
NSM	43.3 (12.1)	44.0 (12.5)	0.6 (9.7, .70)	.006	—	—
Crossed	43.3 (12.0)	43.0 (12.1)	−0.3 (9.6, .84)		50.7 (9.4)	7.8 (12.0, .002)
Did not cross	43.2 (13.2)	47.9 (14.1)	4.0 (9.9, .26)	.24	46.2 (9.8)	2.3 (7.2, .36)
EQ-5D						
TTO						
SIJ fusion	0.44 (0.18)	0.72 (0.22)	0.29 (0.22, <.001)		0.74 (0.20)	0.31 (0.22, <.001)
NSM	0.47 (0.19)	0.52 (0.23)	0.06 (0.28, .17)	< .001	—	—
Crossed	0.45 (0.18)	0.47 (0.20)	0.02 (0.29, .66)		0.73 (0.22)	0.30 (0.26, <.001)
Did not cross	0.53 (0.22)	0.73 (0.20)	0.20 (0.17, .009)	.09	0.74 (0.12)	0.20 (0.17, .008)

[a]EQ-5D, EuroQoL-5D; MCS, mental component summary; NSM, nonsurgical management; PCS, physical component summary; SF-36, Short Form-36; SIJ, sacroiliac joint; TTO, time trade-off; VAS, visual analog scale.
[b]Change from baseline.
[c]Comparison across groups.

higher in the surgery group (1.3 vs 1.1 events; $P = .31$). Over the first 12 months of follow-up, adverse event rates were 1.8 and 1.9 per subject ($P = .45$) in the SIJ fusion and NSM groups, respectively. Over 12 months of follow-up, leg pain and pelvic pain were the most common adverse events (Table 8). Pulmonary events were more common in the NSM group (10.9% vs 2.0%; $P = .04$). Otherwise, there were no statistically significant differences in the rate of individual adverse event categories across treatment groups.

Device-Related Events

Two adverse events were rated as definitely related to the iFuse device. One subject had implant-related impingement on a sacral nerve root requiring immediate revision. Pain resolved promptly on reposition of the device. A second subject developed a hairline (nondisplaced) fracture of the ilium adjacent to the caudal-most implant, diagnosed on CT scan, causing buttock pain 3 to 4 months after the index procedure, possibly related to lifting a heavy object. Pain resolved gradually with conservative treatment. A third subject developed contralateral SIJ pain, which the investigator deemed probably related to the index-side implants as a result of a change in biomechanics related to the placement of the study device (Table 9).

Procedure-Related Events

In the first 6 months (180 days), 16 events (15.7% rate) were probably or definitely related to the surgical procedure and 4 events (8.7% rate) were probably or definitely related to SIJ treatments in the NSM group. Events related to the surgical procedure included neuropathic symptoms (n = 2, 1 case directly attributed to the iFuse implant itself), postoperative medical problems (n = 4, eg, urinary retention, nausea/vomiting, atrial fibrillation), SIJ pain or trochanteric bursitis (n = 4), surgical wound problems (n = 4), iliac fracture (n = 1), and an asymptomatic physical examination finding (n = 1). All events resolved except for ongoing pain in 2 subjects. Three NSM subjects experienced increased back or SIJ pain after physical therapy, SIJ steroid injection, or RFA (1 case each), and another subject had flushing and shortness of breath associated with an SIJ steroid injection. Finally, 1 subject reported worsening SIJ pain related to postoperative rehabilitation after surgery.

Event Severity

In the first 180 days, 30 events were rated as severe (22 in the surgery group and 8 in the NSM group; $P = .60$). In the surgery group, 2 severe events were device related (described above) and 4 were procedure related (1 each of wound hematoma, iliac bone fracture, postoperative impingement of the implant on a sacral nerve root, and postoperative atrial fibrillation/respiratory failure). The 1 severe event in the NSM group attributed to NSM was back pain attributed to physical therapy. Over the course of 12 months of follow-up, a total of 42 severe adverse events occurred. One death occurred unrelated to study treatment (pulmonary fibrosis in an NSM subject).

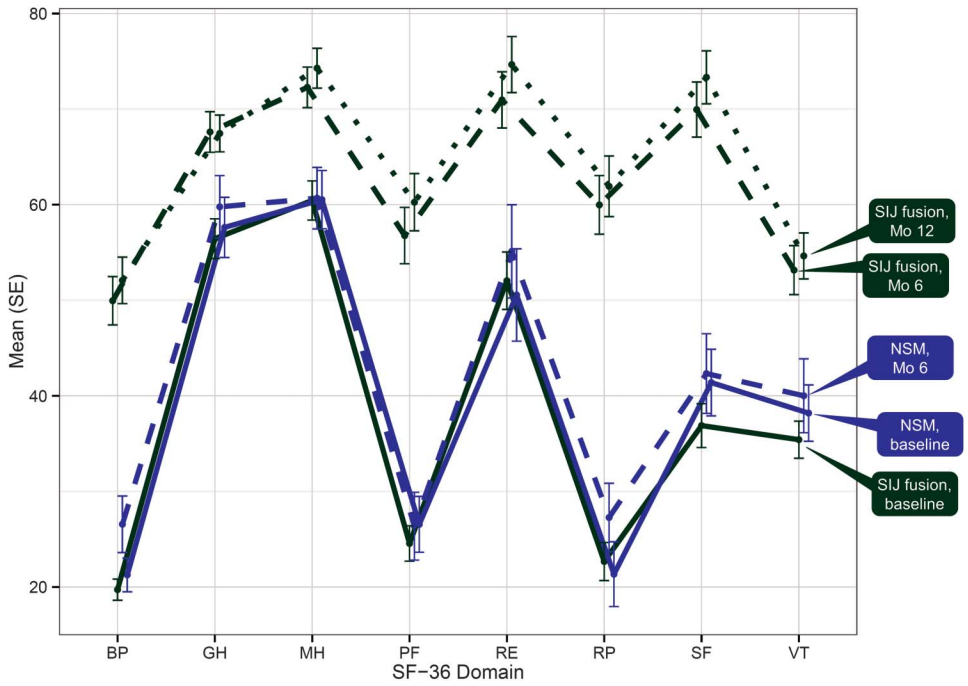

FIGURE 5. *Improvement in Short Form-36 (SF-36) domains by treatment and visit. Values on the x axis values are slightly jittered. Green, sacroiliac joint (SIJ) fusion; blue, nonsurgical management (NSM); solid, baseline; dashed, 6 months; dotted (only SIJ fusion group shown), 12 months. BP, bodily pain; GH, general health; MH, mental health; PF, physical function; RE, role emotional; RP, role physical; SF, social function; VT, vitality.*

DISCUSSION

INSITE is the first randomized clinical trial to directly compare outcomes of surgical and nonsurgical treatment of SIJ dysfunction. The eligibility criteria of the study were designed to select patients on the basis of the best current approach to diagnose SIJ pain, namely historical findings suggestive of SIJ pain (including a positive Fortin finger test), ≥3 positive physical examination maneuver findings that elicited typical pain, and a confirmatory diagnostic anesthetic block of the target joint. Many patients had radiographic findings consistent with SIJ degeneration. Physical examination maneuvers are predictive of a positive response to an SIJ block,[36] and a joint block itself is recommended by multiple practice societies.[47-51] Although this diagnostic strategy represents the current best practice, it should be noted that it does not completely rule out other possible pain generators such as pathology in the hip or spine,[10] which may frequently coexist. This diagnostic strategy represents the most reliable method for identifying this subset of patients, which may represent as many as 15% of patients with chronic lower back pain,[10] confirming that the SIJ is the primary source of pain.

TABLE 7. Adverse Event Rate Per Group[a]

Adverse Events Per Subject	SIJ Fusion (n = 102)	NSM	*P* Value
Time frame			
First 6 mo	1.3 (1.2), 129	1.1 (1.2), 49	.31
First 12 mo	1.8 (1.5), 179	1.9 (1.7), 89[b]	.45

[a]NSM, nonsurgical management; SIJ, sacroiliac joint.
[b]Includes subjects who underwent crossover SIJ fusion surgery.

The primary success end point of the study, a composite of improvement in VAS SIJ pain combined with lack of serious device-related adverse events or reoperation by 6 months, occurred far more commonly in the SIJ fusion group than in the NSM group (81.4% vs 26.1%; bayesian posterior probability of superiority >0.9999). At 12 months, taking into account responses resulting solely from the assigned treatment, clinically important improvements in VAS SIJ pain were seen in 81.6% of SIJ fusion subjects but only 12.5% of NSM subjects ($P < .0001$ for difference). Similarly, for ODI scores, clinically important improvements were observed in 72.4% vs 10.0%, respectively. Only 4 of the original 46 NSM subjects had an improvement of ≥15 points in ODI at month 12 as a result of NSM alone. The threshold chosen for ODI improvement (15 points) was suitably large for this analysis. Collectively, these findings represent a profound, clinically and statistically important difference in overall clinical success rates.

TABLE 8. Adverse Events by Category Over First 12 Months[a]

Category	NSM, n (%)	SIJ Fusion, n (%)	*P* Value
Arm/hand	3 (6.5)	9 (8.8)	.65
Back	8 (17.4)	17 (16.7)	.92
Cardiovascular	1 (2.2)	8 (7.8)	.23
Endocrinological	1 (2.2)	3 (2.9)	.79
Fall	1 (2.2)	2 (2.0)	.93
Foot	0 (0.0)	1 (1.0)	.10
Gastroenterological	5 (10.9)	14 (13.7)	.65
Genitourinary	1 (2.2)	5 (4.9)	.46
Gynaecologic	0 (0.0)	1 (1.0)	>.99
Hematologic	0 (0.0)	1 (1.0)	>.99
Infection	3 (6.5)	5 (4.9)	.70
Leg	23 (50.0)	32 (31.4)	.09
Miscellaneous	4 (8.7)	4 (3.9)	.26
Neck	1 (2.2)	4 (3.9)	.60
Pelvis	21 (45.7)	48 (47.1)	.91
Psychiatric	1 (2.2)	1 (1.0)	.57
Pulmonary	5 (10.9)	2 (2.0)	.04
Shoulder	1 (2.2)	1 (1.0)	.57
Surgical wound	2 (4.3)	5 (4.9)	.89
Trauma	8 (17.4)	16 (15.7)	.81
All	89	179	

[a]NSM, nonsurgical management; SIJ, sacroiliac joint.

The results from our study demonstrate that the clinical success rate associated with minimally invasive SIJ fusion is consistent with retrospective cohort studies,[26-32] a combined multicenter analysis,[33] and a concomitant prospective single-arm multicenter clinical trial.[52,53] The randomized surgery vs nonsurgery design of the study provides Level 1 evidence to the existing body of literature indicating that, for appropriately selected patients, SIJ fusion can meaningfully improve pain, functional capacity (as reflected by ODI scores), and quality of life (as reflected by both EQ-5D and SF-36 scores) compared with NSM. The improvements in these measures were statistically significant, and a majority of subjects also achieved clinically significant benefit. It must be pointed out that, for many patients, SIJ fusion is not a cure because mean posttreatment ODI scores at 6 and 12 months (slightly less than 30 points) remained in the moderately disabled (21-40) range suggested by Fairbank and Pynsent.[37] Several reasons may account for this residual disability, including lack of complete relief after SIJ fusion and competing hip and spinal disease, which were common in our patient population. Disability surveys specific to the SIJ have been developed, but whether they provide additional value is not yet known. However, the 6- and 12-month ODI scores still represent both significant improvement and far less disability than the baseline level of these patients.

TABLE 9. Adverse Events Related to Device or Procedure[a]

Category	NSM (n = 46), n (%[b])	SIJ Fusion (n = 102), n (%)
Related to iFuse implant		
Definitely related	—	2 (2.0)
Probably related	—	1 (1.0)
Total	—	3 (2.9)
Related to NSM or iFuse procedure[c]		
Definitely related	3 (6.5)	6 (5.9)
Probably related	1 (2.2)	10 (9.8)
Total	4 (8.7)	16 (15.7)

[a]NSM, nonsurgical management; SIJ, sacroiliac joint.
[b]Percent reported as number of events divided by number assigned to treatment. Events from first 180 days shown.

The improvement in quality of life after SIJ fusion was substantially larger than that observed for the nonsurgical group. The improvements in physical components of the SF-36 (>30-point improvements in bodily pain, physical function, and role physical subdomains after SIJ fusion vs only a ≤5-point improvement in the NSM group) are larger than those reported at up to 4 years after surgery for lumbar spinal stenosis,[54] similar to those observed at 3 years after surgery for degenerative spondylolisthesis,[55] but smaller than those seen after surgery for lumbar disk herniation.[56] Improvements in SF-36 PCS in the surgical group (12.7 points at 6 months, 13.0 points at 12 months) were in the same range as those documented after lumbar fusion (range, 8-16 points), total knee arthroplasty (7-11 points), and total hip arthroplasty (10-17 points) and slightly larger than those associated with coronary artery bypass graft surgery (6-9 points).[57] These comparisons with commonly accepted spine operations suggest that SIJ fusion has a reasonable place in the therapeutic armamentarium for spine surgeons who treat these patients. In light of the trial data and other supportive evidence, the recent decline in the popularity of open fusion of the SIJ[25] is understandable, and at this point, this more invasive technique is probably best reserved for salvage cases.

Subgroup analysis, undertaken to address concerns about differential effectiveness by particular patient characteristics, revealed no statistically significant differences. Smokers are known to have higher reoperation rates after lumbar laminectomy[58] and lower fusion rates after lumbar fusion.[59,60] In our study, they exhibited somewhat smaller improvements in SIJ pain and ODI, but these differences were not statistically significant. Although smoking may impair bone growth onto titanium implants,[61,62] the effect appeared to be minor. Patients with bilateral SIJ pain responded as well as those with unilateral pain. Similarly, neither a history of lumbar fusion, which is thought to be a risk factor for SIJ degeneration,[12,63] nor the presence of a particular underlying cause of SIJ pain (degeneration vs disruption of the SIJ) significantly attenuated the degree of pain relief and ODI improvement. Nevertheless, we acknowledge that the study was not powered to detect such differences.

Choosing the best treatment options for the nonsurgical control group was a challenge. Using a consensus approach, the study included nonsurgical treatments commonly provided in the

United States despite the limited supportive evidence for these therapies. NSM in this study used a stepped care approach, with interventions provided in order of increasing invasiveness. In the absence of any published clinical studies to guide its delivery, physical therapy was delivered according to recommendations from the American Physical Therapy Association. SIJ steroid injections, although commonly performed, are supported by very limited evidence, and the available randomized trials have examined only periarticular steroid infiltration.[64,65] Two high-quality blinded randomized controlled trials support the use of RFA of sacral nerve roots.[8,9] However, the selection criteria for participation in our study (confirmatory diagnostic SIJ anesthetic block) may vary from those used to deliver RFA (which is typically an anesthetic block of sacral nerve roots). The concordance between these 2 screening techniques has not been elucidated. To the best of our knowledge, the NSM treatment regimen used in our study is the most aggressive nonfusion approach to NSM that we were able to identify in the literature.

In contrast to other well-known spine surgery trials, in which crossover markedly limited the ability to draw conclusions (and necessitated as-treated analyses that remove the benefit of randomization),[66,67] our study had planned crossover at 6 months. We argue that this design was advantageous and enhanced the validity of the trial. Before month 6, there was no early crossover, which enabled a primary end-point comparison (and other comparisons) free from early crossover bias in this early time frame. After month 6, the rate of crossover from nonsurgical to surgical care was high (nearly 80%), providing an additional opportunity to investigate the effectiveness of the surgical procedure. Before crossover, NSM subjects who eventually crossed over derived little, if any, benefit from NSM (mean change in VAS SIJ pain, 5 points on the 0-100 scale; mean change in ODI, 2.1 points). In contrast, as expected, those who did not cross over had experienced substantially better responses. However, very few had complete symptom relief. Crossover SIJ fusion surgery resulted in marked improvements in SIJ pain and disability (mean change in VAS, $>$40 points; mean change in ODI, 26 points) that were similar to changes observed among those initially assigned to surgical treatment. This finding is especially remarkable in that crossover subjects were arguably selected by the trial design to be nonresponders to standard nonsurgical treatment. Although these results suggest that a 6-month delay in providing surgical treatment did not negatively affect the end result, it should be acknowledged that this subset received various nonsurgical treatments (physical therapy, injections, RFA) that expended healthcare resources, estimated at approximately $4500 annually,[68] without any benefit on average. The additional 6 months of pain and disability without clinical improvement in this group should be weighed against the 26.1% of subjects (12 of 46) who had reasonable responses (or did not cross over) to treatment but whose 6- and 12-month pain, ODI, and quality-of-life scores were still elevated. The durability of this response to nonsurgical treatment is unknown. In contrast, response to minimally invasive SIJ fusion with triangular implants was high at 12 months in this study and appears to have favorable long-term response rates at 4.5[32] and 5 years.[31]

Our trial used titanium implants that are triangular in cross section, and typically, 3 devices are placed through a lateral approach to transfix the SIJ. The implants are designed to resist rotation after implantation. Rotation of the study devices, which could increase the risk of loosening and the need for revision, has not been documented to date. The mechanism of action of the device for pain and disability relief is early stabilization, followed by long-term fusion to the sacrum and ilium with bridging bone across the joint; the latter is often seen in imaging studies obtained at long-term follow-up.[31] Radiographic follow-up in the current investigation (derived from a CT scan at the 2-year time point) is pending and will be reported separately. However, it should be emphasized that improvements in pain, disability, and quality of life were evident early in our study and that neither clinical improvements nor bridging bone seems to require full decortication of the SIJ as is routinely done in fusion procedures involving the lumbar, thoracic, and cervical spine. We point out that several devices are now available for minimally invasive SIJ fusion, but given the inherent differences in design and placement approach, the results of our study may not be applicable to these other nontriangular implant systems.

A relatively large number of adverse events were documented in the trial. However, the trial protocol asked investigators to report all negative changes in health (including those in remote areas of the body) as adverse events according to an international clinical trial standard. The numbers of device- and procedure-related adverse events were low, and there were no important differences between the rates of adverse events across groups. Revision surgeries were uncommon and were performed primarily to address implant malposition soon after device placement. To date, 1 trial subject has undergone late revision surgery for persistent pain.

INSITE has both strengths and weaknesses. In an era when surgery vs nonsurgery trials are rare and challenging, the crossover design of INSITE was both practical (given the positive pretrial experience with the device/procedure) and successful (no early crossover, which can make study interpretation challenging[66,69]). INSITE was conducted in accordance with an international clinical trial standard. Follow-up rates were high, and trial compliance was good; moreover, the enrollment rate was high, and the multicenter/multisurgeon aspect of the study supports the generalizability of the treatment effect. One trial weakness is the lack of a sham control (ie, incision and dissection to the ilium, possible drilling, but no implant placement), which is still a rarity for surgical trials because most surgeons and patients are reluctant to participate in such investigations. The study was industry sponsored, as are approximately three-quarters of spine surgery device trials.[70] In the SIJ fusion group, we were unable to determine the separate contributions of the surgical procedure itself as opposed to postoperative rehabilitation to pain and disability relief and improvement in quality of life. However, some patients had minimal amounts of postoperative rehabilitation, and both the surgical and nonsurgical groups received

physical therapy. Moreover, we are unaware of any published high-quality clinical trial evidence that supports the effectiveness of physical therapy for SIJ dysfunction. Although we are reporting relatively early (1 year) outcomes, trial follow-up continues to 2 years. The primary radiographic assessment of the study, CT scan at 2 years, is currently pending. Whereas radiographic outcomes are of great interest, there is growing appreciation that, if treated patients are doing well, then radiographic outcomes may be less relevant. With the increasing recognition of the hazards of the ionizing radiation exposure associated with these scans, we intentionally designed the trial so that only a single postoperative CT scan would be obtained at the 2-year time point.

Finally, given the positive results of the study, the relative cost-effectiveness of surgical vs nonsurgical treatment is also being explored. To this end, this trial was specifically designed to assess the use of healthcare resources, and a cost-utility model is currently being developed.

In summary, this high-quality, Level 1 randomized controlled trial shows that minimally invasive SIJ fusion using porous spray–coated, triangular titanium implants is clinically superior to NSM for the treatment of appropriately selected patients with degenerative sacroiliitis or SIJ disruption. Patients who failed NSM and crossed over to SIJ fusion using the same device also received substantial clinical benefit after surgery.

CONCLUSION

In carefully selected patients with SIJ dysfunction caused by degeneration or disruption of the joint, minimally invasive SIJ fusion using triangular implants placed across the joint provides superior 6-month outcomes compared with NSM. These positive outcomes for pain, disability, quality of life, and satisfaction were maintained at 12 months.

A podcast related to this article can be accessed online (http://links.lww.com/NEU/A771).

Disclosures

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