



EXOGEN 4000+^o Ultrasound Bone Healing System

Caution

Federal Law (U.S.A.) restricts this device to sale, distribution, or use by or on the order of a physician or properly licensed practitioner. The device is only intended for use by the individual for whom it is prescribed. The EXOGEN unit is for single patient use ONLY.

Device Description

The EXOGEN 4000+ device provides non-invasive therapy for healing non-unions and accelerating time to healing of fresh fractures. The EXOGEN Ultrasound Bone Healing System has been designed both for use with conservatively treated fresh fractures and non-unions, or surgically treated non-unions. The device transmits a low intensity ultrasound signal to the fracture site through coupling gel, with little or no sensation felt by the patient during the treatment. The low-intensity pulsed ultrasound has been shown in *in-vitro* and *in-vivo* studies to stimulate cells to produce growth factors and proteins that are important to bone healing. The patient administers treatment at home or at work, once daily, for 20 minutes, or as prescribed by a physician. The device automatically alerts the patient in case of improper application or device performance. The EXOGEN 4000+ Ultrasound Bone Healing System consists of one main operating unit, gel bottles and strap. The main operating unit provides the treatment control circuitry, the primary battery supply, and monitors the operation of the transducer at the fracture site. The signal specifications cannot be changed.

Indications

The EXOGEN 4000+ or any other EXOGEN Ultrasound Bone Healing System is indicated for:

The non-invasive treatment of established non-unions† excluding skull and vertebra.

Accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopaedically managed by closed reduction and cast immobilization.

†A non-union is considered to be established when the fracture site shows no visibly progressive signs of healing.

Contraindications

There are no known contraindications to the use of this device.

Warnings

The safety and effectiveness of the use of this device has not been established for:

- Fractures with post-reduction displacement of more than 50%.
- Pathological fractures due to bone pathology or malignancy.
- Pregnant or nursing women
- Individuals with thrombophlebitis, vascular insufficiency, abnormal skin sensitivity, sensory paralysis, alcoholism and/or nutritional deficiency.
- Individuals receiving steroid, anti-coagulant, prescription non-steroidal anti-inflammatory, calcium channel blocker and/or diphosphate therapy. Individuals using these therapies were excluded from the studies because of the possible effects of these therapies on bone metabolism.
- Non-unions of the vertebra and the skull
- Individuals lacking skeletal maturity
- Fresh fracture locations other than the distal radius or tibial diaphysis
- Fresh fractures that are open Grade II or III or that require surgical intervention or with internal or external fixation or that are not sufficiently stable for closed reduction and cast immobilization.

Precautions

- The device will not correct or alter post-reduction aspects of a fracture such as displacement, angulation or malalignment.
- The EXOGEN device transducer and coupling gel are not sterile and placement on an open wound is not advised.
- The operation of active, implantable devices, such as cardiac pacemakers may be adversely affected by close exposure to the EXOGEN device. The physician should advise the patient or other person in close proximity during treatment to be evaluated by the attending cardiologist or physician before starting treatment with the EXOGEN device.
- Cell phones may cause interference. While the EXOGEN device complies with the limits for Class B digital devices pursuant to Part 15 of the FCC rules, it has not been studied with all brands and models of phone.
- The safety and effectiveness of the EXOGEN device when used for more than one daily 20 minute treatment period has not been studied. Patients in the clinical studies were instructed to apply the device for one treatment period of twenty-minutes each day.
- The age ranges of the patients in the PMA non-union studies were 17-86. The effect of EXOGEN therapy on patients outside this age range has not been studied.
- The age ranges of the patients in the PMA fresh fracture studies were 17-67. The effect of EXOGEN therapy on patients outside this age range has not been studied.
- The safety and effectiveness of the use of this device has been demonstrated for patients followed up over a period of 6.5 years (78 months).

Complications

No device related adverse reactions or medical complications related to the use of this device were reported during the clinical studies. Some patients have experienced mild skin irritation caused by skin sensitivity to the coupling gel. Resolution can be obtained by a change of coupling medium to mineral oil or glycerin. In the distal radius study, one patient complained of pain during treatment but this was resolved by the next follow-up visit and one patient, complaining of pain, withdrew from the study.

Information for Patients

Provide patients with a copy of the Instructions for Use prior to use.

Adverse Events

Unlike conventional (physical therapy) ultrasound devices, the EXOGEN device is incapable of producing harmful temperature increases in body tissue³¹. The output intensity of the device your patient receives is 30 mW/cm² and is typically only 1% to 5% of the output intensity of conventional therapeutic ultrasound devices. The ultrasound intensity is comparable to diagnostic ultrasound (1 to 50 mW/cm²), such as the intensities used in obstetrical sonogram procedures (fetal monitoring). In addition, there is no evidence of non-thermal adverse effects (cavitation).

CLINICAL STUDIES

Treatment of Non-union Fractures

Study design

Three prospectively designed studies, undertaken in the USA, Germany and the Netherlands, were submitted to the FDA³⁵ as the basis for approval of the EXOGEN Ultrasound Bone healing system to treat established non-unions. The studies had a self-paired control design with each non-union case serving as its own control, and with the prior treatment result of failed orthopedic care as the control compared to ultrasound as the only new treatment. The criterion for the definition of non-union cases was the minimum time from fracture of nine months. The primary efficacy outcome was healed due to EXOGEN treatment, as judged clinically (no pain upon palpation or weightbearing) and radiographically (3 out of 4 cortices bridged).

Clinical results

Analyzing the data from Germany, the completed cases had a healed rate of 86% (64/74) with a mean time to a healed fracture of 163±9.4 days. The median heal time was 142 days with a range of 53 to 375 days. The mean fracture age for the healed cases was 494 days with a range of 257-6011 days. The scaphoid non-union heal rate of 33% (2/6) was attributable to the three scaphoid non-union failures that were all more than 10 years in fracture age and, therefore, were very difficult and challenging cases. Cases with metal surgical fixation present during EXOGEN treatment such as those with ORIF (Open Reduction Internal Fixation) and those cases with intramedullary rods had an 88% (21/24) and 100% (16/16) healed rate, respectively. The results of this non-union paired design clinical study established the safety and efficacy of the EXOGEN bone healing system in treating non-unions. This includes cases that had long fracture ages of up to 5 years but suggests that non-unions with over 5 years duration may have a decreased response to ultrasound treatment. The results are summarized in Table 1.

Nolte et al.³¹, reporting on the Netherlands study, confirmed the 86% (25/29) success rate and showed the average heal time to be around 5 months without additional intervention. Average non-union fracture age was 61 weeks. There were high success rates seen with atrophic and oligotrophic non-unions (80% and 92% respectively) where some biological deficiency may contribute to the original non-union. Additionally the application of EXOGEN to hypertrophic non-unions, which might usually be considered as requiring revised treatment to correct fracture instability, was successful in 80% of cases. Success was seen for a range of bones, all types of typical primary fracture management, and across all patient age ranges.

For the United States study, the completed cases group had an 82% (352/429) heal rate.

Other non-union studies:

Frankel and Mizuno³ in their analysis of the 1,546 USA patient non-union registry demonstrated that for patients with risk factors that may impair fracture healing, such as substance abuse, diabetes, vascular problems, or steroid use, there was no significant change in the efficacy of the EXOGEN Ultrasound Bone Healing System. Again high success rates were achieved for all bones, regardless of fracture age, but there was a trend towards higher success rates and faster healing with earlier intervention.

Duarte et al.⁴ presented data from one of the largest cohorts of patients treated with low intensity pulsed ultrasound (1996). 380 nonresponding delayed and non-unions (averaging 14 months old) were treated with the EXOGEN ultrasound signal and achieved an 85% success rate across a range of bones.

Romano et al.³⁶ reported on prospective longitudinal studies in infected non-unions and pseudoarthrosis respectively, suggesting high success rates with low intensity pulsed ultrasound in both situations.

Strauss and Gonya³⁷ described the effects of low intensity pulsed ultrasound on two difficult cases of Charcot non-unions with multiple prior failed surgical procedures. Both cases healed within 5.5 months when treated with the EXOGEN bone healing system.

Acceleration of Conservatively Treated Fresh Distal Radius Fractures

Study design

Placebo-controlled, randomized, double-blind multi-centre study with the prospectively defined primary end-point of a combination of clinical and radiographic healing (4 out of 4 cortices bridged as judged by the blinded principal investigator). 61 patients with conservatively treated cancellous radial fractures were randomized into the EXOGEN treated and control groups (Kristiansen et al.¹⁹).

Patient population and demographics

The demographics of the trial participants were comparable across treatment and control groups with regard to age, sex, fracture characteristics, interval between fracture and commencement of fracture, and duration of follow-up.

Evaluation schedule

Treatment was started within seven days of the fracture, and patients instructed to use the device until the 10 week follow-up visit. Duration of immobilization in the cast was determined by the site investigator. Patients were scheduled to return for follow-up at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16 weeks.

Clinical results

EXOGEN treatment accelerated healing by 38% (61±3.4 days in the active group versus 98±5.2 days in the control group; p<0.0001).

The effect of EXOGEN pulsed low intensity ultrasound on fracture reduction during healing was also assessed. The sub-set of fractures which were satisfactorily reduced having presented with at least 10 degrees of negative volar angulation were analyzed. The active group demonstrated significantly smaller loss of reduction compared to the placebo group (p<0.01).

Acceleration of Conservatively Treated Fresh Tibial Fractures

Study Design

Placebo-controlled, randomized, double-blind multi-centre study with the prospectively defined primary end-point of a combination of clinical and radiographic healing (3 out of 4 cortices bridged as judged by the blinded principal investigator). 67 patients with conservatively treated closed or grade-I open, cortical tibia fractures were randomized into the EXOGEN treated and control groups (Heckman et al.⁷).

Patient population and demographics

The demographics of the trial participants were comparable across treatment and control groups with regard to age, sex, fracture characteristics, interval between fracture and commencement of fracture, duration of follow-up, and days to start weight-bearing.

Evaluation schedule

Treatment was started within seven days of the fracture, and continued for 20 weeks or until the clinical investigator judged the fracture to have healed. All patients were scheduled for follow-up radiographs at 4, 6, 8, 10, 12, 14, 20, 33 and 52 weeks after the fracture. Clinical follow-up evaluations were performed at the time of any cast change (usually at 6 and 10 weeks) and at the follow-up visit when radiographic evaluation indicated the fracture had healed sufficiently to allow removal of the cast.

Clinical Results

EXOGEN treatment induced a 38% acceleration in achieving the prospectively defined primary end-point of a combination of clinical and radiographic healing (96±4.9 days in the active group versus 154±13.7 days in the control group; p<0.0001).

Analysis of fresh fracture studies:

Cook et al.³ pooled the data from the tibia and distal radius studies to analyze the impact of low intensity pulsed ultrasound on the incidence of delayed unions, and on the healing time of smokers. Using a 150 day definition of delayed union, Cook et al.³ determined that the EXOGEN Ultrasound Bone Healing System had a statistically significant effect (p<0.003) on the rate of delayed unions (treated group 6% versus control group 36%). Cook et al.³ also demonstrated a significant reduction in the healing time of smokers for fractures of the tibia and distal radius.

Other fresh fracture studies:

In addition to long bones the effect of the EXOGEN Ultrasound Bone Healing System on fractures of other types of bone has also been clinically studied. A single center, prospective, randomized, double-blind, placebo-controlled study of 40 scaphoid fractures²⁷, demonstrated a statistically significant 31% acceleration in the primary end-point of clinical plus radiographic healing (active 43 days; control 62 days; p<0.01) and 41% improvement in percentage trabecular bridging at 6 weeks

(active 81%, control 55%, p<0.05). A smaller (n=20) single-center, prospective, randomized, double-blind, placebo controlled study of Jones' fractures⁴² showed all actively-treated fractures healed within 56 days whilst only 60% of placebo-treated fractures had healed by 87 days, and 20% had still not healed after 140 days. In addition the actively-treated group reached pain free status 31 to 70 days earlier than the placebo group, and on average took only half the rehabilitation time.

Safety

a. Gross Pathology

Several studies were conducted to assess the safety of the EXOGEN device as part of the FDA summary of safety & effectiveness. Results from a placebo controlled in-vivo study on rabbits with bilateral mid-shaft fibular osteotomies showed no deleterious effects of EXOGEN as evidenced by pathological, hematological, and histological analysis⁴⁰.

b. DNA Analysis

Analysis of the effects of EXOGEN on chromosome of bone marrow cells from a rabbit mid-shaft radius osteotomy reported no measurable, significant, detrimental effects².

c. Temperature

The EXOGEN device's acoustic output is 20 to 100 times less than that of other therapeutic ultrasound devices currently available. An independent university-based medical expert in ultrasound³² concluded the EXOGEN device is incapable of producing temperature elevations greater than 1°C. Such temperature elevations are not considered significant and the potential for detrimental thermal effects is not a concern.

d. Metals & Implants

Several reference articles have focused on conventional therapeutic ultrasound's effect on surgical metallic implants. Lehman et al.²⁰ reported that, based on histological studies, ultrasound applied in the presence of metal implants did not produce any untoward effects. In addition, it has been shown that low intensity ultrasound does not compromise the integrity of a standard orthopaedic stainless steel fixation plate³³. After 30 hours of continuous exposure, no changes or effects could be detected.

Temperature—Gersten²² reported that temperature rises were smaller with metal than with bone at the same depth, and that the presence of metal was not a contraindication to the use of ultrasound.

Migration—Lotsova²³ reported that investigations carried out with Kirschner needles, used as fixation in ultrasound-treated patients did not affect migration of the pins or affect the structural integrity of the pins as determined by metallographic analysis.

Degradation—Skoubo-Kristiansen and Sommer⁴¹ concluded that as a result of ultrasound treatment no effect was observed on fixation screws or the torques necessary for loosening the screws in an in-vivo study. The compatibility of the EXOGEN Ultrasound signal on bioabsorbable screws has also been investigated in-vitro and clinically. Handolin et al.^{15,16} showed treatment with the EXOGEN device had no effect on the mechanical or molecular properties of biodegradable self reinforced poly L-lactide screws and thus biocompatibility between the screws and EXOGEN was good, with no effect on the biodegradation rate.

Apart from Handolin et al.^{15,16}, the studies reported above used ultrasound intensity levels ranging from 0.5 W/cm² to 2 W/cm² and no untoward effects were noted. These intensities are 16 to 60 times higher than the intensity used in the EXOGEN Ultrasound Bone Healing System. It is reasonable to conclude that metal present in a healing fracture would not affect the safety or effectiveness of the EXOGEN Ultrasound Bone Healing System.

e. Clinical

No device-related adverse reactions or medical complications related to the use of this device have been reported during the clinical studies^{3, 4, 6-10, 14, 15, 17-19, 21, 24-31, 33, 36, 39, 42, 43, 47, 49}.

Mode of Action

a. Mode of Action

The low-intensity pulsed ultrasound delivered by the EXOGEN Ultrasound Bone Healing System is a mechanical stimulus. This has been clearly demonstrated by experimental work on cadavers in which tissue around an osteotomized bone moved in response to the ultrasound signal at a frequency of 1kHz, the same frequency as the pulse of the EXOGEN ultrasound signal. Tissue motion has been calculated to be of the order of 0.5nm, approximately 1000 times less than "micro-motion." As well as soft tissue movement, it was demonstrated that the bone moved albeit on a smaller scale³⁸. This work shows stimulation with the EXOGEN Ultrasound Bone Healing System provides motion on a nanometer scale, suggesting the mode of action is independent of fixation methods such as casting or external fixation. Mechanical energy is transformed into biochemical energy by transduction at the cell membrane. One family of cell membrane receptors that are responsible for this transduction are integrins. It has been demonstrated that the EXOGEN ultrasound signal stimulates cells through an integrin pathway³⁰. Within this integrin pathway, cytoskeletal organization, transcription factor activation, gene upregulation, protein synthesis and increased cell proliferation have all been observed.

b. Review information on fracture healing and bone formation

Two review articles^{32,37} have assessed the clinical and basic science evidence for the EXOGEN Ultrasound Bone Healing System. Their analyses suggested the EXOGEN Ultrasound Bone Healing System induced cellular reactions at each phase of fracture healing from inflammation through to endochondral ossification³². In addition, a number of pre-clinical studies have shown acceleration of bone healing with the EXOGEN Ultrasound signal and increased mechanical properties at the fracture site. Pilla et al.^{33,34} in two rabbit bilateral fibular osteotomy placebo-controlled studies, reported statistically significant acceleration of ultrasound treated fibulae versus the placebo side 1.7 and 1.4 times faster, respectively. Wang et al.⁴⁶ and Yang et al.⁴⁵ reported on ultrasound fracture treatment in a model of bilateral closed femoral shaft fractures made in rats and stabilized by a Kirschner wire, serving as an intramedullary rod. Ultrasound treated fractures were shown to be significantly stronger and stiffer than the controls, showing that the stimulatory effect of ultrasound on fracture repair was not inhibited by the presence of a metallic internal fixation device.

Azuma et al.¹, through histological analysis and micro-computed tomography, were able to determine that accelerated fracture healing in the ultrasound-treated group was typical of normal bone healing. EXOGEN Ultrasound accelerated early, mid and late stages of fracture healing with maximum impact achieved when applied throughout the healing process. Takikawa et al.⁴⁴ studied the impact of the EXOGEN Ultrasound Bone Healing System in a hypertrophic non-union model demonstrating 50% resolution in the active group versus 0% in the control group at 6 weeks.

c. Modes

Effects on chondrocytes—Chondrocytes have been shown to respond to the EXOGEN signal by an increase in proteoglycan synthesis (mediated by calcium signaling) and the increase in aggrecan mRNA^{32,40}. **Response of marrow cells to the EXOGEN ultrasound signal**—The EXOGEN signal accelerated the differentiation of mesenchymal cells when cultured in a system designed to promote chondrocytic differentiation².

Periosteal cell response—Human periosteal cell cultures responded to low intensity pulsed ultrasound by increasing expression of alkaline phosphatase, osteocalcin and VEGF. In addition long term treatment (4 weeks of 20 minute daily treatment) increased the level of mineralization in these cultures²².

Osteoblast differentiation—MMP13 and alkaline phosphatase are two enzymes key to the process of mineralization. Unsworth et al.⁴⁵ demonstrated an increase in both these enzymes in MC3T3-E1 cultures after stimulation with EXOGEN ultrasound. Further evidence that ultrasound affects the mineralization process comes from Saito et al.³⁸ who demonstrated accelerated calcium accumulation in MC3T3-E1 cultures. Significant increases (8.6-fold and 3.6-fold higher than untreated controls) were seen at day 25 and day 35 respectively. Collectively the findings of these studies demonstrate that in a pre-osteoblastic culture system EXOGEN low intensity pulsed ultrasound accelerates differentiation along the osteoblastic lineage. Animal studies have shown that such effects in a fracture environment can benefit the formation of a mineralized callus, stabilizing the fracture and increasing the strength of the bone.

Clear evidence exists that the EXOGEN Ultrasound Bone Healing System accelerates the healing process at all stages of fracture repair. In-vitro evidence supports this by demonstrating effects on various cell types, stimulating proteins involved in various biological processes and demonstrating acceleration of some processes in organ culture.

Technical Specifications

Each EXOGEN Ultrasound Bone Healing System device outputs a low intensity pulsed ultrasound signal according to the following specifications:

Ultrasound frequency.....	1.5 ± 5% megahertz (MHz)
Modulating signal burst width.....	200 ± 10% microseconds (µs)
Repetition rate.....	1.0 ± 10% kilohertz (kHz)
Duty factor.....	20%
Effective radiating area.....	3.88± 1% square cm (cm ²)
Temporal average power.....	117 ± 30% milliwatts (mW)
Peak power.....	1.25 ± 30% Watts
Spatial avg. -temporal avg. (SATA).....	30 ± 30% mW/cm ²
Beam non-uniformity ratio (BNR).....	4.0 maximum
Beam type.....	collimated

The EXOGEN 4000+ has the following classifications:

- Internally Powered Equipment
- Type B Applied Part
- Ordinary equipment without protection against ingress of water
- Equipment not suitable for use in the presence of a flammable anaesthetic mixture with air or with oxygen or with nitrous oxide.
- Mode of operation – Intermittent

Guidance and Manufacturer's Declaration – Electromagnetic Emissions and Immunity Testing

Test Description	Published Test Level or Class	Pass/Fail, Comments
Electromagnetic Compatibility Testing		
IEC 60601-1-2:2001		
Summary:		
IEC 61000-4-2 Electrostatic Discharge	±6kV contact discharge ±8kV air discharge	Pass
Testing Report for: Smith & Nephew, Inc.		
IEC 61000-4-3 RF Electromagnetic Field	1kHz sine wave (80% AM) 80-2500 MHz, 3V/m	Pass
Equipment Under Test: EXOGEN 4000+ ^o		
Used for Life Support: No		
IEC 61000-4-4 Electrical Fast Transient/Burst	AC or DC power ports, ±2kV Signal and I/O ports, ±1kV	Not Applicable. The EUT is battery operated. Not Applicable. The EUT cable is less than 3m long.
IEC 61000-4-5 Surge	AC or DC power ports, ±2kV line to ground and ±1kV line to line	Not Applicable. The EUT is battery operated.
Used in shielded enclosure: No		
IEC 61000-4-6 Conducted RF Immunity	AC or DC power ports, 0.15-80 MHz, 3 or 10V Signal and I/O ports, 0.15-80 MHz, 3 or 10V	Not Applicable. The EUT is battery operated. Not Applicable. The EUT cable is less than 3m long.
IEC 61000-4-8 Power frequency Magnetic Field	3A/(rms)/m, @ 50 Hz and 60 Hz	Pass
IEC 61000-4-11 Voltage Dips, Short Interruption	> 95% (10ms), 60% (100ms), 30% (500ms), > 95% (5000ms)	Not Applicable. The EUT is battery operated.
IEC 61000-3-2 Harmonics	Class A, B, C or D	Not Applicable. The EUT is battery operated.
IEC 61000-3-3 Flicker	See standard specifications	Not Applicable. The EUT is battery operated.
CISPR 11 Radiated Emissions	Class B Limits	Pass
CISPR 11 Conducted Emissions	Class B Limits	Not Applicable. The EUT is battery operated.

Test Report # 3066582-27-1-0, November 24, 2004. Testing performed by: Intertek, 1950 Evergreen Blvd, Suite 100, Duluth, GA 30096

Directions for Use

The EXOGEN 4000+ Ultrasound Bone Healing System is administered once daily for 20 minutes per fracture location. Treatment continues until the fracture is determined to be sufficiently healed to discontinue device use. The device transmits a low intensity ultrasound signal to the fracture site through coupling gel.

For detailed instructions, please read the Instructions for Use.

Table 1 Clinical Study results for the FDA reviewed non-union cases – stratification by category variables

Categorical Variable Prior to Start of SAFHS Treatment	Completed Cases Fisher's Exact Probability†					
	Total	Healed	Failed	%Healed	p-value	
Gender:						
Female	30	28	2	93%	0.19	
Male	44	36	8	82%		
Age:						
≤17	1	1	0	100%	0.52	
18-29	12	9	3	75%		
30-49	32	27	5	84%		
50-64	21	19	2	91%		
>65	8	8	0	100%		
Weight (kg):						
<65 kg	12	11	1	92%	0.65	
65-80 kg	35	31	4	89%		
>80 kg	27	22	5	81%		
Fracture age:						
256-365 days	20	19	1	95%	0.001	
366-730 days	27	24	3	89%		
731-1826 days	17	16	1	94%		
≥1827 days	10	5	5	50%		
Total no. surgical procedures combining initial and all subsequent interventions:						
0	20	15	5	75%	0.16	
1	15	12	3	80%		
2	24	23	1	96%		
≥3	15	14	1	93%		
Prior days without surgery (days from last surgical procedure to SAFHS start):						
≤82	9	9	0	100%	0.03	
83-365	39	34	5	87%		
366-730	12	12	0	100%		
≥731	14	9	5	64%		
Bone:						
Tibia/Tibia-Fibula/Fibula	28	26	2	93%	0.03	
Femur	13	12	1	92%		
Radius/Radius-Ulna/Ulna	7	6	1	86%		
Humerus	6	5	1	83%		
Metatarsal	4	4	0	100%		
Other Foot Bones (calcaneus)	1	1	0	100%		
Ankle††	2	1	1	50%		
Scaphoid	6	2	4	33%		
Other Hand Bones (metacarpal)	1	1	0	100%		
Other† (4-clavicle, 1-pelvis, 1-rib)	6	6	0	100%		
†† Tibio-talar arthrodesis						
Long Bone vs. Other Bones:						
Long Bones	59	54	5	92%		0.02
28 tibia						
13 femur						
7 radius						
6 humerus						
4 metatarsal						
1 metacarpal						
Other Bones	15	10	5	67%		
1 calcaneus						
4 clavicle						
1 pelvis						
1 rib						
6 scaphoid						
2 ankle						
Displaced at the start of SAFHS therapy:						
Missing	(5)	(2)	(3)		1.00	
No	56	50	6	89%		
Yes	13	12	1	92%		
Long bone type - Only for long bone cases:						
Missing	(5)	(3)	(2)		0.05	
Metaphyseal	8	6	2	75%		
Diaphyseal	46	45	1	98%		
Initial fracture type:						
Missing	(4)	(2)	(2)		0.16	
Closed	40	34	6	85%		
Open	22	21	1	95%		
Arthrodesis	2	1	1	50%		
Osteotomy	6	6	0	100%		
Fixation present at start of and during SAFHS treatment: IM rod, only for long bone						
No	43	38	5	88%	0.31	
Cases (N=59)						
Open reduction	16	16	0	100%		
No	50	43	7	86%		
Internal fixation (ORIF)	24	21	3	88%		
Yes						
External fixation; only for long bone cases (N=59)	50	46	4	92%		
Yes	9	8	1	89%		
Conservative						
No	58	51	7	88%		
(Cast, splint, brace)						
Yes	16	13	3	81%		
IM rod, or ORIF, or External	10	7	3	70%		
Fixation, or conservative						
Yes	64	57	7	89%		
Prior failed L1/2/3/4/5 therapy:						
No	72	62	10	86%	1.00	
Yes	2	2	0	100%		
Smoking status:						
Missing	(2)	(2)	(0)		0.47	
Never smoked	34	31	3	91%		
Stopped smoking prior to SAFHS start	10	8	2	80%		
Smoker at SAFHS start	28	23	5	82%		
Non-union type:						
Missing	(22)	(17)	(5)		0.57	
Atrophic	41	36	5	88%		
Hypertrophic	11	11	0	100%		

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