Randomized Trial of Reamed and Unreamed Intramedullary Nailing of Tibial Shaft Fractures

By the Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT) Investigators*

Investigation performed at McMaster University, Hamilton, Ontario, Canada

Background: There remains a compelling biological rationale for both reamed and unreamed intramedullary nailing for the treatment of tibial shaft fractures. Previous small trials have left the evidence for either approach inconclusive. We compared reamed and unreamed intramedullary nailing with regard to the rates of reoperations and complications in patients with tibial shaft fractures.

Methods: We conducted a multicenter, blinded randomized trial of 1319 adults in whom a tibial shaft fracture was treated with either reamed or unreamed intramedullary nailing. Perioperative care was standardized, and reoperations for nonunion before six months were disallowed. The primary composite outcome measured at twelve months postoperatively included bone-grafting, implant exchange, and dynamization in patients with a fracture gap of <1 cm. Infection and fasciotomy were considered as part of the composite outcome, irrespective of the postoperative gap.

Results: One thousand two hundred and twenty-six participants (93%) completed one year of follow-up. Of these, 622 patients were randomized to reamed nailing and 604 patients were randomized to unreamed nailing. Among all patients, fifty-seven (4.6%) required implant exchange or bone-grafting because of nonunion. Among all patients, 105 in the reamed nailing group and 114 in the unreamed nailing group experienced a primary outcome event (relative risk, 0.90; 95% confidence interval, 0.71 to 1.15). In patients with closed fractures, forty-five (11%) of 416 in the reamed nailing group and sixty-eight (17%) of 410 in the unreamed nailing group experienced a primary event (relative risk, 0.67; 95% confidence interval, 0.47 to 0.96; p = 0.03). This difference was largely due to differences in dynamization. In patients with open fractures, sixty of 206 in the reamed nailing group and forty-six of 194 in the unreamed nailing group experienced a primary event (relative risk, 1.27; 95% confidence interval, 0.91 to 1.78; p = 0.16).

Conclusions: The present study demonstrates a possible benefit for reamed intramedullary nailing in patients with closed fractures. We found no difference between approaches in patients with open fractures. Delaying reoperation for nonunion for at least six months may substantially decrease the need for reoperation.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Fractures of long bones constitute the majority of emergency operating room procedures in most trauma centers. Among these, tibial fractures are the most common. The National Center for Health Statistics has reported an annual incidence of 492,000 fractures of the tibia and fibula in the United States[1].

Evidence favors the use of intramedullary nails to stabilize diaphyseal fractures of the tibia[2,3]. However, the choice between reamed or unreamed intramedullary nailing of tibial fractures remains controversial[2-4]. Unreamed nailing preserves the endosteal blood supply and may therefore improve fracture-

*The Writing Committee included Mohit Bhandari, MD, MSc, FRCSC, Gordon Guyatt, MD, Paul Tornetta III, MD, Emil H. Schemitsch, MD, Marc Swiontkowski, MD, David Sanders, MD, and Stephen D. Walter, PhD. Please see note preceding reference section for additional details regarding the authors and investigators.

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healing and decrease the risk of infection. Reamed nailing with use of larger nails, while destructive to the endosteal blood supply, affords greater stability[5-16].

A number of prospective, randomized controlled trials have compared the effects of reamed and unreamed intramedullary nailing of lower extremity fractures. Meta-analyses of these trials have suggested large reductions in the risk of nonunion, or failure of the fracture to heal, in association with the use of reamed intramedullary nailing (relative risk, 0.44; 95% confidence interval, 0.21 to 0.93)[3,4,17,18]. Nevertheless, methodological limitations, including lack of concealment, blinding, and standardization of care, have left the efficacy of reamed intramedullary nailing uncertain.

This trial was designed to compare the effects of reamed and unreamed intramedullary nailing approaches. To overcome the limitations of previous studies, the design involved concealed central randomization, blinded adjudication of outcomes (i.e., independent committee review of all primary outcome events), and disallowing reoperation before six months. The present report describes the trial's primary outcome: reoperation and/or autodynamization before one year.

Materials and Methods

Study Design

One thousand three hundred and thirty-nine patients were enrolled in the present trial from July 2000 to September 2005 across twenty-nine clinical sites in Canada, the United States, and The Netherlands. The latest follow-up occurred in September 2006, and final outcomes adjudication was completed in January 2007. The human subjects committees (REB#99-077—Research Ethics Boards/Institutional Review Boards) approved the standardized protocol at each participating site. The study was registered at ClinicalTrials.gov (identifier: NCT00038129). We provide a summary of the methods. A full report of the methodology of the SPRINT (Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures) trial has been published previously[19].

Participating investigators randomized patients by accessing a twenty-four-hour toll-free remote telephone randomization system that ensured concealment. Randomization was stratified by the center and the severity of soft-tissue injury (open, closed, or both open and closed) in randomly permuted blocks of 2 and 4. Patients and clinicians were unaware of block sizes. Patients with a bilateral fracture were assigned the same treatment for both fractures. Patients were allocated to fracture fixation with an intramedullary nail following reaming of the intramedullary canal (the reamed nailing group) or with an intramedullary nail without prior reaming (the unreamed nailing group).

All patients received postoperative care according to the same protocol. The study investigators hypothesized that the benefits of reamed nailing suggested by the previous literature may have been due to a lower threshold for early reoperation in patients managed with unreamed nailing. We therefore disallowed reoperations within the first six months following surgery. Exceptions to the six-month rule included reoperations performed because of infections, fracture gaps, nail breakage, bone loss, or malalignment. Patients, outcome assessors, and data analysts were blinded to treatment allocation. We identified reoperations at each follow-up visit, including at the time of hospital discharge, two weeks after discharge, six weeks postoperatively, and three, six, nine, and twelve months postoperatively.

Eligibility

Eligible men or women were skeletally mature and had sustained a closed or open fracture of the tibial shaft (Tscherne Type 0 to 3, Gustilo Type I to IIIB)[20-23] that was amenable to operative fixation with an intramedullary nail. Inclusion required informed consent. We excluded patients with fractures that were not amenable to either reamed or unreamed intramedullary nailing techniques, those with pathologic fractures, and those who were likely to have problems with maintaining follow-up.

A blinded Outcomes Adjudication Committee adjudicated the eligibility of any randomized patient who did not receive an intramedullary nail; we excluded patients from the final analysis if it was not feasible for them to have received either type of nail. All patients were followed for one year after the time of injury.

Interventions

In the reamed nailing group, intramedullary reaming was conducted over a guidewire with use of cannulated power reamers. All surgeons adhered to the same protocol. First, the surgeon reamed the intramedullary canal until the first detection of "cortical chatter," forming the basis for the nail diameter. Following the appearance of "cortical chatter," the surgeon reamed 1 to 1.5 mm larger than the chosen nail's diameter.

In the unreamed nailing group, the surgeon inserted the nail, without reaming, across the fracture site, with particular attention being paid to the prevention of overdistraction and the achievement of cortical contact of the fracture ends. An upper diameter limit of 10 mm and a nail measuring at least 2 mm less than the diameter measured at the isthmus of the tibia on anteroposterior and lateral radiographs were stipulated.

In both groups, the study required interlocking of all nails, both proximally and distally, as well as the use of at least one proximal locking screw and one distal locking screw.

Standardization of Care for Closed and Open Fractures

To ensure similar perioperative regimens, participating centers standardized key aspects of preoperative and postoperative care for both closed and open fractures.

Closed fractures. First, preoperative antibiotic administration was continued for twenty-four hours postoperatively; specific antibiotic regimens (e.g., gram-positive coverage) were at the discretion of the operating surgeon. Second, cortical contact of the fracture ends guided weight-bearing. If cortical contact was achieved, the patient was allowed to bear weight as tolerated. However, if cortical contact was not achieved, the

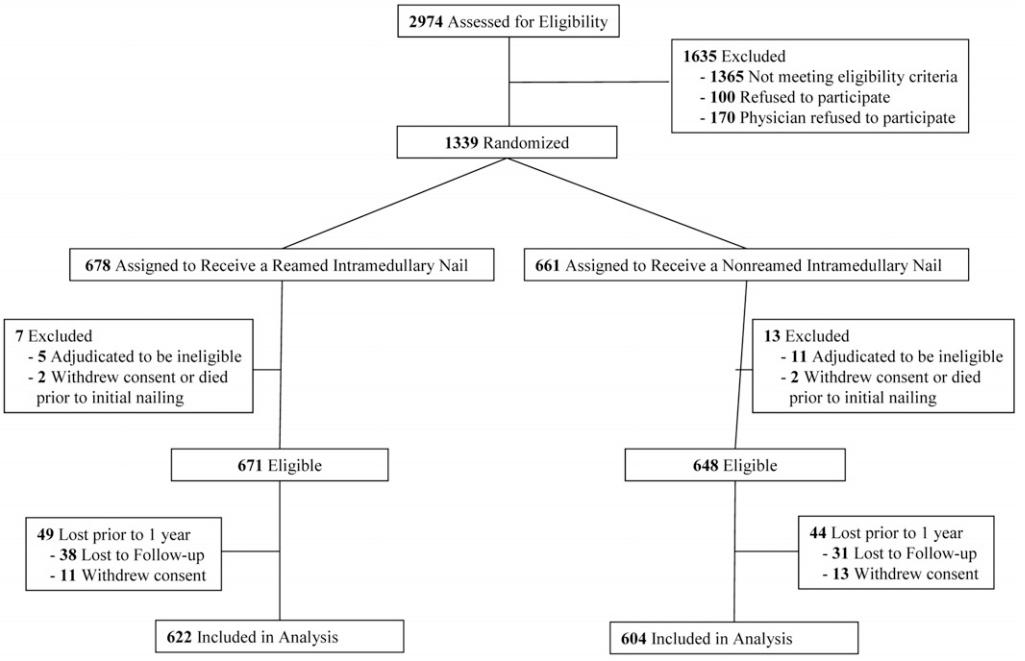

Fig. 1

Flow diagram showing patient enrollment and follow-up throughout the study.

patient was allowed to partially bear weight on the affected limb until a definitive procedure to achieve contact was performed. Third, dynamization of the nail was allowed prior to six months only if the fracture was distracted following nail insertion. Fourth, participating surgeons did not offer stimulation modalities to promote bone growth (such as ultrasound and electrical stimulation) during the one year of follow-up.

Open fractures. First, preoperative intravenous antibiotic administration included a cephalosporin and an aminoglycoside, which were continued for seventy-two hours postoperatively. Specific antibiotics were used at the discretion of the attending surgeon. The recommended guidelines included intravenous administration of cephalosporin (Ancef [cefazolin]) for Gustilo Type-I and II injuries; intravenous administration of Ancef and aminoglycoside (gentamicin) for Type-III injuries; and intravenous administration of Ancef, intravenous administration of gentamicin, and intravenous administration of penicillin for gross contaminated injuries. Second, copious irrigation and débridement of soft tissues and contaminated bone was repeated as necessary. Third, delayed wound closure, split-thickness skin-grafting, or reconstruction with muscle flaps (for Type-IIIB injuries only) was performed by seven days following the initial surgery. Fourth, the protocol regarding weight-bearing, dynamization, and the use of stimulation modalities was the same as that for closed fractures.

Outcomes

We originally defined the primary outcome as a composite including bone-grafting, implant exchange or removal because of a broken nail or deep infection, and débridement of bone and soft tissue because of deep infection. The Centers for Disease Control criteria were used to categorize deep infections.

Ineligible events included reoperations planned at the time of the initial surgery and reoperations to promote healing at the site of fractures with a gap of ≥1 cm after the initial intramedullary nail fixation.

After the first interim analysis in January 2003, when 332 patients had been enrolled, the event rate was substantially lower (13%) than anticipated on the basis of our review of previous studies (32%). In response, we proposed, and both the Data Safety and Monitoring Board and the primary funding agency (Canadian Institutes of Health Research) accepted, adopting an expanded primary composite outcome that included dynamization of the fracture (i.e., interlocking screw removal to allow fracture-site compression with weight-bearing) in the operating room or in the outpatient clinic; removal of locking screws because of hardware breakage or loosening; autodynamization (spontaneous screw breakage leading to dynamization at the fracture site prior to healing); fasciotomy; and drainage of hematomas.

The criteria for undertaking bone-grafting included (1) a fracture gap of ≥1 cm and at least 50% circumferential bone loss at the fracture site or (2) failure of progression of fracture-healing for at least two months, accompanied by clinical symptoms of delayed union (pain, difficulty with weight-bearing). The criteria for exchange intramedullary nailing included (1) a fracture gap of ≥1 cm and at least 50% circumferential bone loss[24] or (2) failure of progression of fracture-healing for at least two months, accompanied by clinical symptoms of delayed union (pain, difficulty with weight-bearing).

TABLE I Patient Characteristics

Characteristic	Total (N = 1226)	Reamed Intramedullary Nailing (N = 622)	Unreamed Intramedullary Nailing (N = 604)
Age* *(yr)*	39.5 ± 16.0	39.1 ± 16.1	39.8 ± 15.9
Sex *(no. of patients)*			
Male	904 (73.7%)	457 (73.5%)	447 (74.0%)
Female	322 (26.3%)	165 (26.5%)	157 (26.0%)
Race *(no. of patients)*			
White	986 (80.4%)	495 (79.6%)	491 (81.3%)
Black	109 (8.9%)	67 (10.8%)	42 (7.0%)
Hispanic	46 (3.8%)	22 (3.5%)	24 (4.0%)
Asian	33 (2.7%)	16 (2.6%)	17 (2.8%)
Native	23 (1.9%)	8 (1.3%)	15 (2.5%)
Other	29 (2.4%)	14 (2.3%)	15 (2.5%)
Mechanism of injury *(no. of patients)*			
Motor-vehicle accident	256 (20.9%)	127 (20.4%)	129 (21.4%)
Pedestrian-motor-vehicle accident	248 (20.2%)	132 (21.2%)	116 (19.2%)
Motorcycle accident	143 (11.7%)	71 (11.4%)	72 (11.9%)
Crush injury	64 (5.2%)	31 (5.0%)	33 (5.5%)
Fall	355 (29.0%)	179 (28.8%)	176 (29.1%)
Twist	57 (4.6%)	28 (4.5%)	29 (4.8%)
Direct trauma (penetrating)	18 (1.5%)	8 (1.3%)	10 (1.7%)
Direct trauma (blunt)	84 (6.9%)	46 (7.4%)	38 (6.3%)
Snowmobile accident	1 (0.1%)	0 (0.0%)	1 (0.2%)
History of surgery to the affected lower limb† *(no. of patients)*			
Yes	73 (6.0%)	36 (5.8%)	37 (6.1%)
No	1150 (94.0%)	584 (94.2%)	566 (93.9%)
Smoking history† *(no. of patients)*			
Current smoker	406 (33.3%)	200 (32.4%)	206 (34.2%)
Previous smoker	104 (8.5%)	54 (8.7%)	50 (8.3%)
Nonsmoker	711 (58.2%)	364 (58.9%)	347 (57.5%)
Side of fracture *(no. of patients)*			
Isolated			
Left	546 (44.5%)	279 (44.9%)	267 (44.2%)
Right	658 (53.7%)	328 (52.7%)	330 (54.6%)
Bilateral	22 (1.8%)	15 (2.4%)	7 (1.2%)
Type of fracture *(no. of patients)*			
Open	392 (32.0%)	202 (32.5%)	190 (31.5%)
Closed	826 (67.4%)	416 (66.9%)	410 (67.9%)
Both open and closed‡	8 (0.7%)	4 (0.6%)	4 (0.7%)
Medications *(no. of patients)*			
Nonsteroidal anti-inflammatory medication	87 (7.1%)	44 (7.1%)	43 (7.1%)
Oral steroids	7 (0.6%)	4 (0.6%)	3 (0.5%)
Anticonvulsants	32 (2.6%)	16 (2.6%)	16 (2.6%)
Anticoagulants	153 (12.5%)	81 (13.0%)	72 (11.9%)
Statins	16 (1.3%)	12 (1.9%)	4 (0.7%)
Bone stimulators *(no. of patients)*	34 (2.8%)	13 (2.1%)	21 (3.5%)
Isolated fractures§ *(no. of patients)*	825 (67.3%)	418 (67.2%)	407 (67.4%)

*The values are given as the mean and the standard deviation. †Missing some data. ‡These fractures are categorized as ''Open'' in outcomes analyses and reflect bilateral injuries. §No other appendicular long-bone injuries.

TABLE II Fracture Characteristics*

Characteristic	Total (N = 1248)	Reamed Intramedullary Nail (N = 637)	Unreamed Intramedullary Nail (N = 611)
Type of fracture *(no. of fractures)*			
Open	406 (32.5%)	210 (33.0%)	196 (32.1%)
Gustilo[21] Type I	108 (26.6%)	46 (21.9%)	62 (31.6%)
Gustilo[21] Type II	161 (39.7%)	86 (41.0%)	75 (38.3%)
Gustilo[21] Type IIIA	107 (26.4%)	59 (28.1%)	48 (24.5%)
Gustilo[21] Type IIIB	30 (7.4%)	19 (9.0%)	11 (5.6%)
Closed†	842 (67.5%)	427 (67.0%)	415 (67.9%)
Tscherne[23] Type 0 or 1	688 (81.8%)	349 (81.9%)	339 (81.7%)
Tscherne[23] Type 2 or 3	153 (18.2%)	77 (18.1%)	76 (18.3%)
Location in shaft† *(no. of fractures)*			
Proximal	31 (2.5%)	17 (2.7%)	14 (2.3%)
Proximal-middle	103 (8.3%)	57 (9.0%)	46 (7.6%)
Middle	303 (24.5%)	150 (23.8%)	153 (25.2%)
Distal-middle	529 (42.7%)	270 (42.8%)	259 (42.7%)
Distal	272 (22.0%)	137 (21.7%)	135 (22.2%)
Bone loss *(no. of fractures)*			
Yes	91 (7.3%)	48 (7.5%)	43 (7.0%)
No	315 (25.2%)	162 (25.4%)	153 (25.0%)
Not applicable (closed fracture)	842 (67.5%)	427 (67.0%)	415 (67.9%)
AO Classification[22] *(no. of fractures)*			
A1 (simple fracture, spiral)	216 (17.3%)	110 (17.3%)	106 (17.3%)
A2 (simple fracture, oblique)	254 (20.4%)	120 (18.8%)	134 (21.9%)
A3 (simple fracture, transverse)	231 (18.5%)	119 (18.7%)	112 (18.3%)
B1 (wedge fracture, spiral wedge)	87 (7.0%)	48 (7.5%)	39 (6.4%)
B2 (wedge fracture, bending wedge)	172 (13.8%)	87 (13.7%)	85 (13.9%)
B3 (wedge fracture, fragmented wedge)	110 (8.8%)	56 (8.8%)	54 (8.8%)
C1 (complex fracture, spiral)	32 (2.6%)	19 (3.0%)	13 (2.1%)
C2 (complex fracture, segmental)	91 (7.3%)	46 (7.2%)	45 (7.4%)
C3 (complex fracture, irregular)	55 (4.4%)	32 (5.0%)	23 (3.8%)

*Based on 1248 fractures in 1226 patients. †Missing some data.

Follow-up

We assessed reoperation rates prior to hospital discharge and at the time of follow-up visits. An Adjudication Committee including five orthopaedic traumatologists, a clinical trialist, and the study statistician (M.B., G.G., D.S., M.S., P.T. III, E.H.S., S.D.W.), blinded to allocation, adjudicated all outcomes. The committee resolved disagreement through discussion. All centers sent digital photographs of the required radiographs to the SPRINT Methods Center via e-mail. In addition, site coordinators mailed all relevant hospital records. All relevant blinded patient records (DataFax [Hamilton, Ontario, Canada] case report forms, chart notes, and radiographs) were posted on a specially designed, and password-protected, Internet website for adjudication. We were concerned that the size of the nail would be sufficient to unmask the allocation of treatment as the nails used for unreamed fixation are smaller in diameter. To mask the allocation of treatment, we photo-edited to crop the digital radiograph to include only the fracture site.

For fractures that surgeons reported to have <50% cortical contact between the fracture ends, all adjudicators determined the fracture gap. For all suspected study events, adjudicators judged the size of the fracture gap, whether the reoperation was planned or unplanned, the appropriateness of reoperation, and whether the suspected study event was an actual study event. Any disagreements were resolved by means of a conference call. If the adjudicators could not reach consensus, additional information was requested from the participating site to clarify areas of uncertainty. All decisions made by the committee were final.

At the time of trial close-out, we visited all participating sites and conducted a site audit to identify any missed events. All radiographs were reviewed to confirm broken-screw events.

Sample Size

Our original target sample size of 900 patients (450 per treatment arm) was based on two-sided significance testing

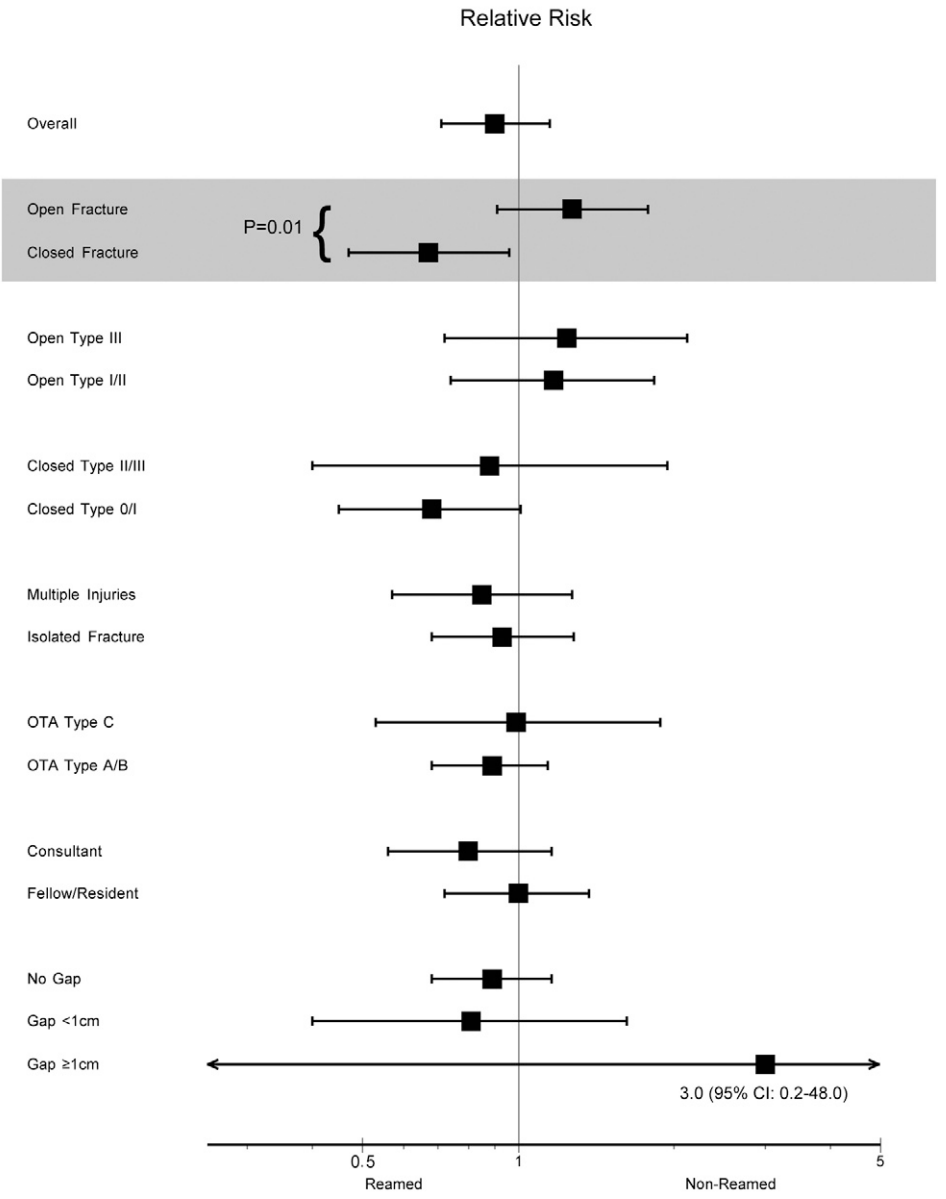

Fig. 2

Results of subgroup analysis.

with $\alpha = 0.05$. The original sample size had a power of 80% to detect a relative risk of 0.80 for event rates as low as 25%.

We planned a single interim analysis after 300 patients had completed one year of follow-up and with use of an O'Brien-Fleming stopping rule. This statistical stopping rule was used to determine the significance level for the interim analysis. We set the significance level at 0.0006 for our interim analysis, thus maintaining a significance level of 0.05 for the final analysis. After the interim analysis of 332 enrolled patients who had been followed for one year (performed in January 2003), the lower-than-anticipated event rates led to an upward revision of the target sample size to 1200 patients (600 per arm). The sample size was based on the expanded definition of reoperation and ensured >80% power for a relative risk of 0.63 for event rates of >13%. To ensure 1200 patients with full follow-up, we enrolled 1339 patients.

Statistical Analyses

Our primary analysis included only patients for whom complete one-year follow-up data were available. We excluded patients with no follow-up data to avoid assumptions about outcome rates among patients who were lost. We further analyzed patients in the arm to which they originally had been randomized, regardless of which treatment they received, according to the intention-to-treat principle.

We compared the proportion of patients with a reoperation in the reamed nailing group with the proportion of patients with a reoperation in the unreamed nailing group at one

TABLE III Study Events in Patients with Closed Fractures

Event	Total* (N = 826)	Reamed* (N = 416)	Unreamed* (N = 410)	Relative Risk†	P Value
Primary events (reoperation)‡	113	45	68	0.67 (0.47 to 0.96)	0.03
Secondary events§	10	6	4	2.10 (0.49 to 8.96)	0.30
Reoperations in response to infection, irrespective of the size of the fracture gap	16	9	7	1.37 (0.48 to 3.93)	0.56
Fasciotomy for treatment of postoperative compartment syndrome (in a separate procedure from the intramedullary nailing)	7	6	1	5.92 (0.71 to 49.33)	0.06
Bone-grafting	4	2	2	0.95 (0.12 to 7.38)	0.96
Implant exchange for union	16	6	10	0.57 (0.21 to 1.53)	0.26
Fasciotomy for treatment of intraoperative compartment syndrome (in the same procedure as the intramedullary nailing)	7	1	6	0.15 (0.02 to 1.25)	0.04
Dynamization in the operating room	24	8	16	0.50 (0.22 to 1.15)	0.09
Removal of locking screws because of hardware breakage or loosening of screws	1	1	0	2.90 (0.12 to 68.33)	0.33
Dynamization in the outpatient clinic	5	2	3	0.82 (0.15 to 4.49)	0.82
Autodynamization	41	12	29	0.42 (0.22 to 0.80)	0.01

*The values are given as the number of patients. †Relative risks are based on a stratified proportions analysis. The 95% confidence interval is given in parentheses. ‡Bone-grafting in a patient with full cortical continuity, implant exchange for union in a patient with full cortical continuity, implant removal for union in a patient with full cortical continuity, reoperation in response to a local infection, bone-grafting in a patient with a fracture gap of <1 cm, implant exchange in a patient with a fracture gap of <1 cm, implant removal in a patient with a fracture gap of <1 cm, dynamization in a patient with a fracture gap of <1 cm, removal of locking screws due to hardware breakage or loosening of screws, treatment of wound necrosis in the presence of infection, fasciotomy for the treatment of intraoperative compartment syndrome, fasciotomy for the treatment of postoperative compartment syndrome, autodynamization (failure of the screw-bone construct [i.e., broken or bent screws] that dynamizes the fracture), draining of a hematoma, failure of the construct (broken nail). §Infections that were treated nonoperatively.

year of follow-up with use of a Mantel-Haenszel stratified analysis. We stratified according to center and whether the fracture was open or closed. We compared the occurrence of not only the primary composite outcome but also each component of that composite in the two groups.

Additional analyses, employing log binomial regression, controlled for the influence of patient and surgical factors that were hypothesized a priori to be associated with the risk of reoperation. The results of the stratified analyses were similar to those of the adjusted analyses; we present only the former.

Subgroup analyses were conducted with use of tests for interactions; all were specified a priori. Our subgroup analysis of primary interest was the comparison between open fractures and closed fractures. Additional subgroup hypotheses included the impact of treatment in patients with multiple trauma as compared with those with isolated fractures; OTA classification[22] type C as compared with types B and A; operations performed by surgeons as compared with fellows and residents; and fracture gaps of >1 cm as compared with <1 cm as compared with no gap.

The Steering and Writing Committees developed and recorded two interpretations of the results on the basis of a blinded review of the primary outcome data (treatment A compared with treatment B), with one assuming that A was the reamed nailing group and another assuming that A was the unreamed nailing group. The Writing Committee deliberated before data analysis to determine the key analyses and presentation format for the primary SPRINT publication.

Results

Eligibility

Of the 2974 patients who were screened for eligibility, 1319 were randomized in the study; of these, 1226 (93%) completed the final one-year follow-up visit and were included in the analysis (Fig. 1). The characteristics of the patients who were lost to follow-up were similar to those of the patients who were followed for one year (see Appendix). More patients who were allocated to the unreamed nailing arm underwent reamed nailing than the reverse (fifty-five compared with eight; $p < 0.001$). Overall, the management of 96% of the patients adhered to key aspects of the protocol with regard to the use of proximal and distal interlocking screws, the use of perioperative antibiotics, the use of intramedullary nail fixation, and the guidance of weight-bearing status on the basis of cortical continuity after nailing.

Patient Characteristics

Included patients were predominantly male, white, and involved in motor-vehicle-related accidents (Table I). Open fractures represented 33% of the total (Table II). The two groups were similar

TABLE IV Study Events in Patients with Open Fractures

Event	Total* (N = 400)	Reamed* (N = 206)	Unreamed* (N = 194)	Relative Risk†	P Value
Primary events (reoperation)†	106	60	46	1.27 (0.91 to 1.78)	0.16
Secondary events§	9	4	5	0.67 (0.18 to 2.41)	0.53
Reoperations in response to infection, irrespective of the size of the fracture gap	35	19	16	1.27 (0.67 to 2.40)	0.46
Fasciotomy for treatment of postoperative compartment syndrome	5	3	2	1.39 (0.24 to 8.07)	0.71
Bone-grafting	13	7	6	1.23 (0.39 to 3.84)	0.72
Implant exchange for union	24	12	12	0.90 (0.42 to 1.91)	0.78
Fasciotomy for treatment of intraoperative compartment syndrome	3	2	1	1.75 (0.15 to 20.36)	0.65
Incision and drainage of hematoma	3	0	3	0.32 (0.05 to 1.88)	0.07
Implant removal for union	3	3	0	3.82 (0.45 to 32.62)	0.09
Dynamization in the operating room	30	17	13	1.17 (0.58 to 2.36)	0.66
Dynamization in the outpatient clinic	1	0	1	0.36 (0.02 to 8.03)	0.34
Autodynamization	17	9	8	1.12 (0.43 to 2.91)	0.82
Failure of construct (broken nail)	1	0	1	0.20 (0.01 to 4.40)	0.19

*The values are given as the number of patients. †Relative risks are based on a stratified proportions analysis. The 95% confidence interval is given in parentheses. ‡Bone-grafting in a patient with full cortical continuity, implant exchange for union in a patient with full cortical continuity, implant removal for union in a patient with full cortical continuity, reoperation in response to a local infection, bone-grafting in a patient with a fracture gap of <1 cm, implant exchange in a patient with a fracture gap of <1 cm, implant removal in a patient with a fracture gap of <1 cm, dynamization in a patient with a fracture gap of <1 cm, removal of locking screws due to hardware breakage or loosening of screws, treatment of wound necrosis in the presence of infection, fasciotomy for the treatment of intraoperative compartment syndrome, fasciotomy for the treatment of postoperative compartment syndrome, autodynamization (failure of the screw-bone construct [i.e., broken or bent screws] that dynamizes the fracture), draining of a hematoma, failure of the construct (broken nail). §Infections that were treated nonoperatively.

with respect to key prognostic variables (Table I). The groups also were similar with regard to aspects of the operative procedure, including the nail manufacturer and the antibiotic protocol, and with regard to postoperative weight-bearing (see Appendix).

Primary Composite Outcome: Reoperation and/or Autodynamization within One Year

One hundred and five patients (16.9%) in the reamed nailing group and 114 patients (18.9%) in the unreamed nailing group experienced a primary outcome event (relative risk, 0.90; 95% confidence interval, 0.71 to 1.15; p = 0.40). Reoperations to promote fracture-healing were performed in 106 patients; fifty-seven (4.6%) of all 1226 patients underwent implant exchange or a bone-grafting procedure because of nonunion. Forty-eight (45%) of the 106 patients (including twenty-three in the reamed nailing group and twenty-five in the unreamed nailing group; p = 0.97) had a reoperation before six months. The treatment effect differed across subgroups only between closed and open fractures (test for interaction, p = 0.01) (Fig. 2). Therefore, we present the results separately for closed and open fractures.

Primary Events in Patients with Closed Tibial Shaft Fractures

One hundred and thirteen patients with a closed tibial shaft fracture (13.7%; 95% confidence interval, 12% to 16%) underwent a reoperation within the first year. Of the patients with closed fractures, forty-five (11%) of 416 in the reamed nailing group and sixty-eight (17%) of 410 in the unreamed nailing group experienced a primary event (relative risk, 0.67; 95% confidence interval, 0.47 to 0.96; p = 0.03). This difference was largely due to differential rates of dynamization, particularly autodynamization (Table III).

Primary Events in Patients with Open Tibial Shaft Fractures

One hundred and six patients with an open tibial shaft fracture (26.5%; 95% confidence interval, 22% to 31%) underwent a reoperation or autodynamization within the first year. Of the patients with open fractures, sixty (29%) of 206 in the reamed nailing group and forty-six (24%) of 194 in the unreamed nailing group experienced a primary event (relative risk, 1.27; 95% confidence interval, 0.91 to 1.78; p = 0.16) (Table IV).

Adverse Events

Eighteen patients died, nine had a deep venous thrombosis, seven had a pulmonary embolus, and one had sepsis. Significantly more deaths occurred in the reamed nailing group than in the unreamed nailing group (fourteen compared with four; p = 0.03). In the reamed nailing group, the causes of death included cardiorespiratory complications (six patients), major

head injury (five), sepsis (two), and suicide (one). In the unreamed nailing group, the causes of death included cardiorespiratory complications (two patients), major head injury (one), and suicide (one). Blinded adjudicators classified all deaths as unrelated to the intramedullary nailing procedure.

Discussion

This trial of 1226 patients with fractures of the tibial shaft demonstrates a substantially lower reoperation rate as compared with those reported in previous studies (see Appendix).

We identified a decrease in the rate of combined end points of surgical intervention and autodynamization in association with reamed intramedullary nailing in patients with closed fractures. This difference was largely due to differences in the rate of dynamization, particularly autodynamization (Table III). We found a nonsignificant increase in the combined end point rate in association with reamed intramedullary nailing in patients with open fractures.

The strengths of the present study included a large sample size; multiple participating surgeons and centers; strategies to reduce bias that included centralized randomization that ensured concealment; blinding of patients and data analysts; independent, blinded adjudication of eligibility and of outcome; and a proscription of reoperation for nonunion before six months.

The subgroup effect in open as compared with closed fractures meets most criteria for a credible subgroup analysis[25]. We generated the hypothesis a priori and found a large and significant ($p = 0.01$) difference in effect size in this within-study comparison. Although the hypothesis was one of a number tested, it was the subgroup hypothesis of primary interest as reflected in our decision to stratify randomization according to open as compared with closed fractures. The interaction is biologically plausible because preservation of the endosteal blood supply may be more important in open than in closed fractures.

The present trial had several limitations. Participating surgeons had relatively more experience with the reamed nailing approach: a survey of 139 study investigators (seventy-four of whom responded) demonstrated that, in the year before the trial started, they had performed a median of twelve reamed procedures and a median of two unreamed procedures[26]. The much larger number of patients who crossed over from unreamed to reamed nailing as opposed to crossing over from reamed to unreamed (fifty-five as compared with eight) suggests that a differential expertise bias may have played a role in our study. To the extent that surgeons had superior skills in reamed nailing, our results are biased against the unreamed nailing procedure. The actual nail sizes differed by only 1 mm between the unreamed and reamed nailing groups. Whether this reflects a change in practice toward the insertion of larger canal-filling nails without reaming is debatable; however, it may account to some extent for the lack of differences between treatment groups.

Our inability to blind surgeons risked further bias. Of the survey respondents, 87% believed that a reamed procedure was superior[26]. Belief in the superiority of the reamed procedure could lead to a differential threshold for reoperation. To limit the extent of surgeon bias in favor of the reamed intramedullary nailing technique, we proscribed discretionary procedures for the treatment of delayed union during the first six months after surgery. This strategy proved to be effective: although adherence to our six-month proscription-of-reoperation rule was far from complete (55%), the number of premature procedures was virtually identical in the reamed and unreamed nailing groups.

We used a composite end point complicated by large gradients in importance to patients[27,28]. The significant result favoring reamed nailing in the group with closed fractures was largely driven by the least important outcomes, dynamization and particularly autodynamization, which some surgeons consider to be of little importance. Of the 113 events in patients with closed fractures, seventy were dynamizations, of which forty-one were autodynamizations. We were limited in our ability to further explore screw diameter and screw breakage because this information was not collected in our SPRINT dataforms. While our focus on a composite outcome leaves us unable to claim or refute benefit for any of the components of the composite, the present trial provides little evidence of the superiority of the reamed nailing procedure for the treatment of closed fractures in terms of the more patient-important components.

One might view our 93% rate of follow-up as a strength; five previous small randomized trials[29-33] lost as many as 38% of patients (average rate of loss to follow-up, 12%). We used multiple strategies in this trial to ensure maximum follow-up[34,35]. On the other hand, our results are sensitive to extreme assumptions regarding the distribution of events in patients lost to follow-up.

A systematic review of the literature identified five previous meta-analyses[2-4,17,18] and four randomized trials (published between 1996 to 2004)[29-32] comparing reamed and unreamed tibial nailing. Of the five meta-analyses, one study evaluated open fractures, two studies evaluated closed fractures, and two studies evaluated a mix of open and closed fractures.

The patients in the present study experienced much lower event rates in comparison with those in previous randomized controlled trials. Surgeons in the present study substantially reduced the use of bone-grafting and implant exchanges (5% compared with 10.6%) and dynamizations (5% compared with 13.2%) (see Appendix). Explanations for the substantially reduced event rate in the present study include standardization and thus optimization of perioperative care and disallowing reoperation before six months. The lower rates of screw failure and subsequent autodynamization in the present study are likely a reflection of implant improvements since 1996.

Our finding of fewer dynamizations, and fewer autodynamizations, in association with reamed nailing of closed fractures is strongly supported by those of previous studies. In two studies that evaluated closed fractures[32,33], differential rates of dynamizations represented 56% and 69% of the

total events, with no significant differences being seen in terms of major reoperations such as bone-grafting procedures, implant exchanges, or procedures performed for the treatment of infections.

The magnitude of the effect favoring reamed nailing for the treatment of closed fractures is considerably less in the present study than in previous studies, and we found a nonsignificant increase in events in association with reamed nailing of open fractures. The most likely explanation for this difference is the much more rigorous design of the current study. Previous investigators did not use central randomization (raising serious questions about concealment of the treatment allocation[36]), did not utilize central blinded adjudication, and did not blind the data analysis. Finally, and perhaps most importantly, they made no effort to avoid differential criteria for reoperation in the reamed and unreamed nailing groups.

Our results have important implications for clinical practice. First, they suggest that surgeons may reduce operations by allowing increased time for these fractures to heal. Second, to the extent that patients and clinicians see dynamization as important, the results support the use of reamed nailing for closed fractures. The optimal nailing technique for open fractures remains uncertain.

Appendix

(eA) Tables showing aspects of the surgical procedure, including nail manufacturer, antibiotic protocol, and postoperative weight-bearing, event rates, and loss to follow-up rates, are available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD/DVD (call our subscription department, at 781-449-9780, to order the CD or DVD). ■

NOTE: Details regarding the authors and investigators are provided below.

Author Contributions:

Writing Committee: The Writing Committee (Mohit Bhandari, MD [Chair]; Gordon Guyatt, MD; Paul Tornetta III, MD; Emil H. Schemitsch, MD; Marc Swiontkowski, MD; David Sanders, MD; and Stephen D. Walter, PhD) assumes responsibility for the overall content and integrity of the manuscript. Drs. Bhandari and Guyatt, as Principal Investigators, had full access to the study data and take responsibility for its integrity and the accuracy of the analyses.

Study concept and design: Mohit Bhandari, Gordon Guyatt, Stephen Walter, Paul Tornetta III, Emil H. Schemitsch, David Sanders, Marc Swiontkowski.

Analysis and interpretation of data: Mohit Bhandari, Gordon Guyatt, Stephen Walter, Paul Tornetta III, Emil H. Schemitsch, David Sanders, Marc Swiontkowski.

Drafting of the manuscript: Mohit Bhandari, Gordon Guyatt.

Critical revision of the manuscript for important intellectual content: Mohit Bhandari, Gordon Guyatt, Stephen Walter, Paul Tornetta III, Emil H. Schemitsch, David Sanders, Marc Swiontkowski.

Statistical analysis: Stephen Walter, Gordon Guyatt, Mohit Bhandari.

Obtained funding: Mohit Bhandari, Gordon Guyatt, Marc Swiontkowski, Paul Tornetta III.

Study supervision: Mohit Bhandari, Gordon Guyatt, Stephen Walter, Paul Tornetta III, Emil H. Schemitsch, David Sanders, Marc Swiontkowski.

SPRINT Investigators:

The following persons participated in the SPRINT Study:

Study trial co-principal investigators: Mohit Bhandari, Gordon Guyatt.

Adjuc Committee: Gordon Guyatt (Chair), Mohit Bhandari, David Sanders, Emil H. Schemitsch, Marc Swiontkowski, Paul Tornetta III, Stephen Walter.

Central Adjudication Committee: Gordon Guyatt (Chair), Mohit Bhandari, David W. Sanders, Emil H. Schemitsch, Marc Swiontkowski, Paul Tornetta III, Stephen Walter.

Steering / Adjudication / Writing Committee: Gordon Guyatt (Chair), Mohit Bhandari, David W. Sanders, Emil H. Schemitsch, Marc Swiontkowski, Paul Tornetta III, Stephen Walter.

SPRINT Methods Center staff:

McMaster University, Hamilton, Ontario: Sheila Sprague, Diane Heels-Ansdell, Lisa Buckingham, Pamela Leece, Helena Viveiros, Tashay Mignott, Natalie Ansell, Natalie Sidorkewicz.

University of Minnesota, Minneapolis, Minnesota: Julie Agel.

Data Safety and Monitoring Board (DSMB): Claire Bombardier (Chair), Jesse A. Berlin, Michael Bosse, Bruce Browner, Peter O'Brien, Brenda Gillespie, Alan Jones.

Site Audit Committee: Julie Agel, Sheila Sprague, Rudolf Poolman, Mohit Bhandari.

Investigators:

London Health Sciences Centre / University of Western Ontario, London, Ontario: David W. Sanders, Mark D. MacLeod, Timothy Carey, Kellie Leitch, Stuart Bailey, Kevin Gurr, Ken Konito, Charlene Bartha, Isolina Low, Leila V. MacBean, Mala Ramu, Susan Reiber, Ruth Strapp, Christina Tieszer.

Sunnybrook Health Sciences Centre / University of Toronto, Toronto, Ontario: Hans J. Kreder, David J.G. Stephen, Terry S. Axelrod, Albert J.M. Yee, Robin R. Richards, Joel Finkelstein, Michael Ford, Wade Gofton, John Murnaghan, Joseph Schatztker, Beverly Bulmer, Lisa Conlan.

Hospital du Sacre Coeur de Montreal, Montreal, Quebec: G. Yves Laflamme, Gregory Berry, Pierre Beaumont, Pierre Ranger, Georges-Henri Laflamme, Sylvain Gagnon, Michel Malo, Julio Fernandes, Marie-France Poirier.

St. Michael's Hospital / University of Toronto, Toronto, Ontario: Emil H. Schemitsch, Michael D. McKee, James P. Waddell, Earl R. Bogoch, Timothy R. Daniels, Robert R. McBroom, Milena R. Vicente, Wendy Storey, Lisa M. Wild.

Royal Columbian Hospital / University of British Columbia, New Westminster / Vancouver, British Columbia: Robert McCormack, Bertrand Perey, Thomas J. Goetz, Graham Pate, Murray J. Penner, Kostas Panagiotopoulos, Shafique Pirani, Ian G. Dommisse, Richard L. Loomer, Trevor Stone, Karyn Moon, Mauri Zomar.

Wake Forest Medical Center / Wake Forest University Health Sciences, Winston-Salem, North Carolina: Lawrence X. Webb, Robert D. Teasdall, John Peter Birkedal, David Franklin Martin, David S. Ruch, Douglas J. Kilgus, David C. Pollock, Mitchel Brion Harris, Ethan Ron Wiesler, William G. Ward, Jeffrey Scott Shilt, Andrew L. Koman, Gary G. Poehling, Brenda Kulp.

Boston Medical Center / Boston University School of Medicine, Boston, Massachusetts: Paul Tornetta III, William R. Creevy, Andrew B. Stein, Christopher T. Bono, Thomas A. Einhorn, T. Desmond Brown, Donna Pacicca, John B. Sledge III, Timothy E. Foster, Ilva Voloshin, Jill Bolton, Hope Carlisle, Lisa Shaughnessy.

Wake Medical Center, Raleigh, North Carolina: William T. Obremskey, C. Michael LeCroy, Eric G. Meinberg, Terry M. Messer, William L. Craig III, Douglas R. Dirschl, Robert Caudle, Tim Harris, Kurt Elhert, William Hage, Robert Jones, Luis Piedrahita, Paul O. Schricker, Robin Driver, Jean Godwin;

Vanderbilt University Medical Center, Nashville, Tennessee: William T. Obremskey, Philip James Kregor, Gregory Tennent, Lisa M. Truchan, Marcus Sciadini, Franklin D. Shuler, Robin E. Driver, Mary Alice Nading, Jacky Neiderstadt, Alexander R. Vap.

MetroHealth Medical Center, Cleveland, Ohio: Heather A. Vallier, Brendan M. Patterson, John H. Wilber, Roger G. Wilber, John K. Sontich, Timothy Alan Moore, Drew Brady, Daniel R. Cooperman, John A. Davis, Beth Ann Cureton.

Hamilton Health Sciences, Hamilton, Ontario: Scott Mandel, R. Douglas Orr, John T.S. Sadler, Tousief Hussain, Krishan Rajaratnam, Bradley Petrisor, Mohit Bhandari, Brian Drew, Drew A. Bednar, Desmond C.H. Kwok, Shirley Pettit, Jill Hancock, Natalie Sidorkewicz.

Regions Hospital, St. Paul, Minnesota: Peter A. Cole, Joel J. Smith, Gregory A. Brown, Thomas A. Lange, John G. Stark, Bruce A. Levy, Marc F. Swiontkowski, Mary J. Garaghty, Joshua G. Salzman, Carol A. Schutte, Linda Tastad, Sandy Vang.

University of Louisville School of Medicine, Louisville, Kentucky: David Seligson, Craig S. Roberts, Arthur L. Malkani, Laura Sanders, Carmen Dyer, Jessica Heinsen, Langan Smith, Sudhakar Madanagopal, Linda Frantz-Bush.

Memorial Hermann Hospital, Houston, Texas: Kevin J. Coupe, Jeffrey J. Tucker, Allen R. Criswell, Rosemary Buckle, Alan Jeffrey Rechter, Dhiren Shaskikant Sheth, Brad Urquart, Thea Trotscher.

Erie County Medical Center / University of Buffalo, Buffalo, New York: Mark J. Anders, Joseph M. Kowalski, Marc S. Fineberg, Lawrence B. Bone, Matthew J. Phillips, Bernard Rohrbacher, Philip Stegemann, William M. Mihalko, Cathy Buyea.

University of Florida at Jacksonville, Jacksonville, Florida: Stephen J. Augustine, William Thomas Jackson, Gregory Solis, Sunday U. Ero, Daniel N. Segina, Hudson B.

Berrey, Samuel G. Agnew, Michael Fitzpatrick, Lakina C. Campbell, Lynn Derting, June McAdams.

Academic Medical Center, Amsterdam, The Netherlands: J. Carel Goslings, Kees Jan Ponsen, Jan Luitse, Peter Kloen, Pieter Joosse, Jasper Winkelhagen, Raphaël Duivenvoorden.

University of Oklahoma Health Science Center, Oklahoma City, Oklahoma: David C. Teague, Joseph Davey, J. Andy Sullivan, William J.J. Ertl, Timothy A. Puckett, Charles B. Pasque, John F. Tompkins II, Curtis R. Gruel, Paul Kammerlocher, Thomas P. Lehman, William R. Puffinbarger, Kathy L. Carl.

University of Alberta / University of Alberta Hospital/Royal Alexandra Hospital, Edmonton, Alberta: Donald W. Weber, Nadr M. Jomha, Gordon R. Goplen, Edward C.O. Masson, Lauren A. Beaupre, Karen E. Greaves, Lori N. Schaump.

Greenville Hospital System, Greenville, South Carolina: Kyle J. Jeray, David R. Goetz, David E. Westberry, J. Scott Broderick, Bryan S. Moon, Stephanie L. Tanner.

Foothills General Hospital, Calgary, Alberta: James N. Powell, Richard E. Buckley, Leslie Elves.

Saint John Regional Hospital, Saint John, New Brunswick: Stephen Connolly, Edward P. Abraham, Trudy Steele.

Oregon Health and Sciences University, Portland, Oregon: Thomas Ellis, Alex Herzberg, George A. Brown, Dennis E. Crawford, Robert Hart, James Hayden, Robert M. Orfaly, Theodore Vigland, Maharani Vivekaraj, Gina L. Bundy.

University of California, San Francisco, San Francisco General Hospital, San Francisco, California: Theodore Miclau III, Amir Matityahu, R. Richard Coughlin, Utku Kandemir, R. Trigg McClellan, Cindy Hsin-Hua Lin.

Detroit Receiving Hospital, Detroit, Michigan: David Karges, Kathryn Cramer, J. Tracy Watson, Berton Moed, Barbara Scott.

Deaconess Hospital Regional Trauma Center and Orthopaedic Associates, Evansville, Indiana: Dennis J. Beck, Carolyn Orth.

Thunder Bay Regional Health Science Centre, Thunder Bay, Ontario: David Puskas, Russell Clark, Jennifer Jones.

Jamaica Hospital, Jamaica, New York: Kenneth A. Egol, Nader Paksima, Monet France.

Ottawa Hospital–Civic Campus, Ottawa, Ontario: Eugene K. Wai, Garth Johnson, Ross Wilkinson, Adam T. Gruszczynski, Liisa Vexler

Mohit Bhandari, MD, MSc, FRCSC
SPRINT Methods Center,
Department of Clinical Epidemiology and Biostatistics,
McMaster University, 293 Wellington Street North, Suite 110,
Hamilton, ON L8L 2X2, Canada.
E-mail address: bhandam@mcmaster.ca

Gordon Guyatt, MD
Stephen D. Walter, PhD
Department of Clinical Epidemiology and Biostatistics,
Health Sciences Centre, Room 2C12 (G.G.) and 2C16 (S.W.),
1200 Main Street West, Hamilton, ON L8N 3Z5, Canada

Paul Tornetta III, MD
Department of Orthopaedic Surgery, Boston Medical Center,
818 Harrison Avenue, Dowling 2 North, Boston, MA 02118-2393

Emil H. Schemitsch, MD
St. Michael's Hospital, 55 Queen Street E., #800, Toronto,
ON M5C 1R6, Canada

Marc Swiontkowski, MD
Department of Orthopaedic Surgery, 2450 Riverside Avenue,
Minneapolis, MN 55454

David Sanders, MD
London Health Sciences Centre,
4th Floor, Westminster Tower,
800 Commissioners Road East,
London, ON N6A 4G5, Canada

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