

## **Research Plan and Supporting Data**

### **A. Specific Aims**

The primary aim of this investigation is the evaluation of functional outcomes of patients with diaphyseal femur fractures treated with intramedullary nails, documenting these patient based outcomes at various time points (3, 6, 12, 24 months). Secondary aims include subgroup analyses of multitrauma patients with diaphyseal femur fractures versus those patients with isolated femoral shaft fractures. The null hypothesis for this subgroup analysis posits that no significant differences will be identified in outcomes or in the time curve of the recovery. Our additional secondary aim is the comparison of the three types of intramedullary nailing techniques commonly utilized for the surgical management of these diaphyseal femur fractures. Anterograde piriformis, anterograde trochanteric, and retrograde starting points are all commonly employed by orthopaedic surgeons managing these patients. The null hypothesis for this subgroup analysis proposes that patient based outcome and time curve of the recovery are both independent of the nail technique employed.

The clinical relevance of this investigation will resonate with all orthopaedic surgeons who provide care in all types of emergency departments, from small community hospitals to level 1 trauma centers. No longer is simply providing patients and families a projection of chances of achieving union with intramedullary nailing an adequate informed discussion. Increasingly, orthopedists and patients expect meaningful patient based outcome information well beyond the technical success rates of the procedure. Evaluation of the results of the validated patient based outcome measures SF-36 and the SMFA, as well as a published activity return questionnaire, will objectively document these functional outcome parameters. Discussion of these findings with patients will allow the treating orthopedist to accurately inform the patient regarding functional prognosis and time curve for recovery. Should differences be identified in the subgroup analyses, risk/benefit information will be useful to the surgeon and the patient or family in choosing treatment technique and in understanding additional difficulties related to multitrauma patients with femur fractures. Additionally, the outcomes data may provide new directions regarding case management and rehabilitation instructions. Should specific technique-related issues become apparent, early physical therapy directed at mitigating these effects may be useful. Vocational rehabilitation efforts may be identified to be more helpful in certain patients with certain constellations of injuries. Other predictions of timely return to activity will be better informed and may facilitate planning for the patient and the patient's employment issues.

### **B. Background and Significance**

Reamed intramedullary nailing remains the gold standard in the treatment of femoral diaphyseal fractures. This treatment is associated with an extremely high union rate and a low complication rate. The current generation of femoral nails allows treatment of all femoral diaphyseal fractures, with technique-specific instrumentation facilitating anterograde piriformis, anterograde trochanteric and retrograde starting points. For decades the outcomes from intramedullary nailing studies have focused on union rates and evaluations of complications such as shortening, iatrogenic comminution and malrotation. (Winqvist RA, et al 1984) Union rates now approach 100% when reamed canal-filling anterograde or retrograde femoral nails are used in the treatment of femoral shaft fractures. (Brumback 1988, Wolinsky 1999, Ostrum 2000, Ricci WM 2005)

Also for decades it was believed that patients with multiple injuries including femoral shaft fractures were “too sick to operate on,” and these patients were kept at bedrest in skeletal traction. Most authors recommended a delay in surgery until 10-14 days after injury in these multiply injured patients (Wickstrum 1967 and Smith 1964). Pioneering work then appeared in the early 1970s suggesting that immediate stabilization of femur fractures dramatically reduced problems of traumatic pulmonary failure when compared to traditional nonoperative or delayed surgical management of the diaphyseal femur injuries in multiply injured patients. (Seibel 1985 and Riska 1977) The body of evidence grew to support a greater benefit of early stabilization, particularly in the more severely injured patients (Johnson 1985). A randomized trial (Bone 1989) found that patients with high ISS scores stabilized early (within 24 hours) had less mortality and a significantly lesser rate of pulmonary complications including pneumonia and ARDS, when compared to the patients in the delayed stabilization group.

As improvements in critical care medicine allowed better support of the multiply injured patients, more aggressive surgical approaches became possible. Yet the dogma of early total care for these severely injured patients also came into question with reports criticizing the methods and conclusions of the articles supporting early total care (Reynolds 1995). A multicenter study of 1127 patients with femur fractures found an unexpectedly high rate of pulmonary complication among patients stabilized early with reamed intramedullary nailing. (Ecke 1985) Many observers felt that adverse pulmonary outcomes occurred more frequently in the presence of severe chest injuries following severe shock states or in patients in uncertain clinical conditions (Nast 1990, Pape 1993). Unexpected deterioration was found in selected subgroups of multiply injured patients, ultimately termed borderline patients. Investigators attempted to describe the borderline patient on the basis of clinical and laboratory findings (Pape 1999 and 2000), contending that such patients cannot initially withstand significant surgical trauma in addition to their initial trauma. Damage control orthopedic protocols evolved from this and other work (Scalea 2000). Damage control protocols typically advocate provisional stabilization of femoral shaft fractures with external fixation in borderline patients. Although normalization of physiological parameters, including base deficit, lactate levels, hemodynamic parameters, and lung and renal function, is typically used to determine when definitive stabilization can be performed in these borderline patients, the best timing of secondary intervention remains unclear. A large scale prospective cohort is currently proposed among this multicenter trauma group to evaluate functional outcome and systemic complications in these multiply injured patients with associated diaphyseal femur fractures.

Patient driven outcome measures have advanced the understanding and practice of orthopedic trauma in a number of areas. Sobering results continue to be reported from the Lower Extremity Assessment Project (LEAP) study group. (MacKenzie 2005) Among 397 patients with high energy lower leg and hindfoot trauma that had undergone either amputation or limb salvage reconstruction, physical functioning deteriorated between 2 and 7 years after the injury. These patients had scores indicative of substantial disability, leading the authors to suggest priority be given to efforts to improve post-acute-care services that address secondary conditions.

A recently completed study of 1226 patients with tibia shaft fractures has documented the one year patient based outcomes and return to activities for patients treated with tibial intramedullary nails.

(The SPRINT Study Group 2007) The outcomes were determined using SF-36, the SMFA and an activity return questionnaire at time intervals up to one year after injury. While the technique of intramedullary insertion, either reamed or unreamed, did not yield any differences in outcome parameters, patients with open fractures and multiply injured patients indeed had statistically worse outcomes, more dysfunction and lower rates of return to work than the comparison patients with closed or isolated injuries. Furthermore, patients sustaining tibial shaft fractures do not return to their pre-injury status based on validated outcome assessments or return to activity instruments by one year after injury. Even the best results, seen in the isolated closed fracture group, demonstrated only a 54% return to sporting activities and a 79% back to work rate at one year.

These and other functional outcome studies of significant lower extremity trauma patients highlight the importance of similar studies for femoral shaft fracture patients. While many studies demonstrate union rates over 95%, no studies adequately and systematically evaluate patient based outcomes for a large group of femoral shaft fracture patients. The multicenter trauma group will be collecting data on the damage control orthopedics cohort of multiply injured patients with femoral shaft fractures. Based on the SPRINT study group results and the LEAP study group results, multiply injured patients likely fare significantly worse than patients with isolated femoral shaft fractures. Achieving osseous union at 6 or 9 months in either of these subgroups is unlikely to necessarily equate with return of normal preinjury function.

Of significant but secondary interest to orthopedists is the potential relationship of intramedullary nail technique to functional outcome. Modern studies using reamed canal-filling techniques with specific instrumentation and nails designed for a given entry point demonstrate uniformly high union rates. However concern remains regarding the three various nail techniques. Some authors have documented high union rates and low complication rates using trochanteric nail insertion sites for the treatment of femoral shaft fractures (Ricci 2005). Ease of gaining a starting point and utility in patients with particularly large body habitus are often touted as advantages of the trochanteric entry point over the conventional piriformis fossa entry point. Other authors have compared retrograde and antegrade femoral intramedullary nailing (Ostrum 2000). Most work has concentrated on operative complications, set up and starting point times as well as overall operative times. Some groups have found increased incidence of knee pain following retrograde femoral nailing and hip pain following piriformis antegrade femoral nailing. In a comparison of trochanteric versus piriformis nailing (Ricci 2006), this group found less fluoroscopic time was required for the trochanteric entry starting point, particularly in obese patients. Both groups had initial decline in their lower extremity functional measures. Overall, the vast majority of data from these comparative studies focus on technique related outcomes including operative time, fracture alignment, fracture healing and fluoroscopic time. Little systematic focus is paid to patient based outcome measures. This current study will evaluate potential differences among all three types of intramedullary nail techniques. Most authors have suggested that long term outcome studies are necessary to better delineate the functional consequences of these starting point techniques. (Moed 1999)

### **C. Preliminary Studies/Progress Report**

A preliminary investigation at the co-PI's institute evaluated antegrade versus retrograde femoral nailing. That work compared 51 antegrade starting point nail patients to 67 retrograde starting point nail patients. The patients were followed at regular intervals and evaluated by an activity questionnaire and SF-12. More patients in the retrograde nail group required hardware removal for

local knee complaints. However when statistical correction for multiple outcome measurements was made, no variable was significant. Retrograde nailing was felt to be comparable to the gold standard of anterograde nailing. However significant disability was present in both groups between the time of union and the one year followup. (Kin K, Brown D, Tornetta P, unpublished data)

## **D. Research Design and Methods**

### Overall Design

The study will be set up as a longitudinal cohort study in 390 patients with femoral shaft fractures with a priori groups that will be compared. The primary outcome is patient based recovery over time to be evaluated using multiple validated outcome tools for physical function, psychological well being, and return to activities. The secondary analysis will be a comparison of patients with isolated injuries versus those with multiple injuries.

Based on the outcomes being investigated, a randomized trial is not necessary or possible. The effect of other variables will be evaluated by a regression analysis. This will include the effect of education, work status, smoking, technique of nailing, alignment, motion, pain, etc on outcome.

### Eligibility

The inclusion and exclusion criteria are designed to represent all patients with a femur shaft fracture. Specific criteria are listed below in tables 1 and 2.

### Surgical Care and Standardization

Investigators will follow their local standard of care regarding operative technique, but all patients will be treated with reamed statically locked intramedullary nails. The ultimate timing of surgery will be up to the treating physician. Postoperative protocols will be standardized regarding weightbearing rehabilitation. Patients with axially stable fractures will be allowed immediate full weightbearing, while those with unstable injuries will be partial weightbearing until there is bridging callus, and then full weightbearing will be permitted. Immediate range of motion exercises will be instituted, with CPM (continuous passive motion) being permitted on an as needed basis by the surgeon.

### Data Management and Confidentiality

A web based data entry system will be employed. This system is being developed in part for several other studies that are already in progress (randomized trial of distal femur fractures being treated with nails vs plates, and a similar study in proximal tibias). Thus, the cost for this additional study is partly born by the initial development costs. Similar demographic and outcome forms are being used which will allow us to get the system up and running by adding only the MMSE, fracture characteristics, and surgical report forms. The system will house all data in a HIPAA compliant fashion and allow for statistical analysis by a precontracted team. Likewise, all radiographs will be housed for independent review if needed, which will be determined by the steering committee. A

DSMB will be formed to review the blinded data at appropriate intervals. A list of the centers that have committed in writing to the project is included in this proposal.

### Study specifics:

Each of 20 sites will screen for inclusion and exclusion parameters. All patients will be treated by the standard of care in that institution. Standard demographic and surgical data will be obtained. Informed consent of the patients and/or surrogates will be obtained for use of this data and for

enrollment into a standard follow-up scheme based on the requirements of each individual institution. Inclusion criteria are listed in Table 1, exclusion criteria in Table 2. The parameters being recorded and the timing of same are listed in Table 3 and the follow-up grid is seen in Table 4. As seen in Table 3, each parameter will be recorded at specific time periods. Data will be kept in a HIPAA compliant system and be entered by the individual sites via a protected web based system that will be monitored daily for missing data and errant values.

#### Minimizing Loss to Follow Up

Loss to followup will be minimized by the use of established protocols. We have developed a primer for all centers to use to help properly screen patients, and strategies to maintain and re-establish contact with them. It will be of great import to get followup until the plateau of outcomes occurs, or at least for one year.

#### Outcome Measures

Our primary outcome will be to fully describe the physical and mental recovery of patients with femur shaft fractures treated using the current standard of care (reamed interlocked intramedullary nails). This will be done by using multiple time point assessments and validated patient based outcome measures {(SF12, SMFA, EQ-5D, and MMSE (cognitive function evaluation))}. Nothing more than graphic and descriptive statistics are needed for this, the most important outcome measure.

The SF-36 questionnaire was developed from the Medical Outcomes Study. It is a self-administered, 36-item questionnaire that measures health-related quality of life in eight domains. Both physical and mental summary scores can be obtained. Each domain is scored separately from 0 (lowest level) to 100 (highest level). The instrument has been extensively validated and has demonstrated good construct validity, high internal consistency, and high test-retest reliability (Ware 1992). Our decision to use the SF-12 over other available instruments was based on its widespread use in orthopaedics, its use in previous studies evaluating fracture outcomes, and the strong evidence of validity.

The EuroQol 5D (<http://gs1.q4matics.com/EuroqolPublishWeb/>) is a standardized instrument for use as a measure of health outcome (Euroqol Group, 1990). The EQ-5D self-report questionnaire (EQ-5D) essentially consists of two pages comprising the EQ-5D descriptive system and the EQ VAS (visual analogue scale). The EQ-5D descriptive system comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. The EQ-5D has been used in previous studies involving patients with fractures and has been extensively validated. It is

cognitively simple, taking only a few minutes to complete.

One secondary aim will entail evaluation of the subgroup of patients with multitrauma versus those with isolated fractures. Functional outcome differences between isolated and multitrauma patients in a large, multicenter trial of tibial shaft fractures (SPRINT, n=1339 patients randomized) identified 10% absolute differences in SF-36 physical function summary scores. Patients with isolated tibia fractures had superior outcomes to those who were multiply injured;  $44.7 \pm 11$  vs  $40 \pm 12$  for the SF36 PCS { $p < 0.001$  95%CI=(3-6.3)}. Extrapolating these findings to the proposed study of femoral shaft

fractures, we anticipate similar or greater differences in function. Our proposed sample, therefore, will be sufficiently powered to evaluate this à priori subgroup.

### Sample Size and Analysis Considerations

Another secondary aim will assess differences in function (SF-36 physical function component summary score) across 3 different Nailing Approaches (RN, PN, TN). Assuming a 5 point difference in scores (10% absolute difference) across any of the approaches, a standard deviation of 12 points, a study power of 80%, an adjusted alpha of 0.02, our study requires at least 116 patients per study arm (total sample size: 348). Adjusting for a 10% loss of follow up, we will recruit 390 patients for the study (130 patients/arm).

Our final aim will be to look at other possible measures that affect outcome, such as education, type of work, smoking, etc. This will be done by a regression analysis of all factors that demonstrate an apparent effect using simple comparative measures. Finally, any interaction among the outcome measures will be sought. In particular, correlation between the MMSE and the general health measures will be evaluated.

The data capture will be inclusive, rather than exclusive such that other factors that may play a role in the initial physiologic or later functional outcomes of these patients may be sought. A full listing is seen in the data point listing table.

### Definitions:

*Femur shaft fracture:* Fracture that occurs within the diaphysis of the femur.

*Multiple trauma patient:* patients who sustain additional injuries of at least a grade 2 abbreviated injury score. This will include additional skeletal injuries that do not affect ISS.

*Anterograde piriformis nailing:* A nail placed from the top of the bone to the bottom via an entry site in the piriformis fossa.

*Anterograde trochanteric nailing:* A nail placed from the top of the bone to the bottom via an entry site on the greater trochanter.

*Retrograde nailing:* A nail placed from the bottom of the bone to the top using an intraarticular knee portal.

## **CONTINUATION PAGE**

### Table 1: Inclusion Criteria

1. 18-65 years of age
2. Fracture of the femoral diaphysis amenable to intramedullary nail fixation
3. Surgeon agreed to randomize patient
4. Informed consent obtained
5. Patient is English speaking

### Table 2: Exclusion Criteria

1. Age < 18 or > 65
2. Ipsilateral proximal femur fracture (femoral neck, intertrochanteric, subtrochanteric)
3. Ipsilateral distal femur metaphyseal fracture with or without intercondylar extension
4. Fracture with vascular injury (Gustillo Type IIIC injury) requiring repair
5. Pathological fracture
6. Known metabolic bone disease
7. Multiple traumatic injuries of the ipsilateral lower extremity (hip, femur, tibia) that would compromise outcome assessment
8. Periprosthetic fracture
9. Retained hardware or existing deformity in the affected limb that would complicate IM nailing
10. Symptomatic hip and/or knee arthritis
11. Soft tissue injuries compromising treatment method with nail
12. Initial surgical delay greater than 2 weeks for closed fractures or 24 hours for open fractures
13. Contralateral femur fracture (bilateral injury) or lower extremity injury that would compromise outcome assessment
14. Immunocompromise
15. Unable to comply with postoperative rehabilitation protocols or instructions (i.e. head injured or mentally impaired)
16. Current or impending incarceration
17. Unlikely or unwilling to follow-up
18. Nonoperative femoral shaft fracture

**Table 4: Patient Follow-up Grid**

<i>Case Report Form</i>	<i>Completed By</i>	<i>PreOp</i>	<i>Day of Surgery</i>	<i>Hospital Course</i>	<i>1 mo. PostOp</i>	<i>3 mos. PostOp</i>	<i>6 mos. PostOp</i>	<i>12 mo. PostOp</i>	<i>24 mo. PostOp</i>
Inclusion/Exclusion Criteria	Physician	X							
Patient Information	Physician	X							
Fracture Characteristics	Physician	X							
SF-36	Patient	X					X	X	X
SMFA	Patient	X					X	X	X
EQ-5D	Patient	X				X	X	X	X
MMSE	Physician / Patient	X			X	X	X	X	X
Surgical Summary	Physician		X						
Hospital Course Summary	Physician			X					
Follow-up Clinical Evaluation	Physician				X	X	X	X	
Adverse Event Form	Physician								X
<b>Radiographic Images</b>		<i>PreOp</i>	<i>PostOp</i>			<i>3 mos. PostOp</i>	<i>6 mos. PostOp</i>	<i>12 mo. PostOp</i>	
Femur A/P	Physician	X	X				X	X	

						X			
Femur Lateral	Physician	X	X			X	X	X	

## E. Human Subjects

### Patient Population

Patients will be recruited primarily from the emergency departments and orthopedic clinics of the co-investigator sites. Over 20 orthopaedic surgeons are participating in the study and are primarily located at academic medical centers in the Northeast, South, Southeast, Midwest, and Northwest regions of the United States, and in Canada (Ontario). The outcome assessments are only validated in English and therefore English speaking patients are a requirement for inclusion. Bone maturity is also necessary for inclusion and thus the study will exclude children. The ethnic background and health status of the patients are expected to be representative of the patient population at the participating sites.

Age range: 18-65  
Sex: Male and Female  
Ethnicity: Representative of site's patient population  
Health Status: Representative of site's patient population

### Inclusion Criteria

1. 18-65 years of age
2. Fracture of the femoral diaphysis amenable to intramedullary nail fixation
3. Surgeon agreed to randomize patient
4. Informed consent obtained
5. Patient is English speaking

Patients may have undergone previous surgical interventions either for placement of a spanning external fixator and/or debridement of open fracture wounds. This may have been done at the eventual treating institution or not. That is, the patient could represent a referral of a diaphyseal femur fracture, which had undergone previous debridement and spanning external fixator placement.

### Exclusion Criteria

We exclude individuals from the study if they have the following characteristics:

1. Age < 18 or > 65
2. Ipsilateral proximal femur fracture (femoral neck, intertrochanteric, subtrochanteric).
3. Ipsilateral distal femur metaphyseal fracture with or without intercondylar extension
4. Fracture with vascular injury (Gustillo Type IIIC injury) requiring repair
5. Pathological fracture
6. Known metabolic bone disease
7. Multiple traumatic injuries of the ipsilateral lower extremity (hip, femur, tibia) that would compromise outcome assessment
8. Periprosthetic fracture
9. Retained hardware or existing deformity in the affected limb that would complicate IM nailing
10. Symptomatic hip and/or knee arthritis



11. Soft tissue injuries compromising treatment method with nail
12. Initial surgical delay greater than 2 weeks for closed fractures or 24 hours for open fractures
13. Contralateral femur fracture (bilateral injury) or lower extremity injury that would compromise outcome assessment
14. Immunocompromise
15. Unable to comply with postoperative rehabilitation protocols or instructions (i.e. head injured or mentally impaired)
16. Current or impending incarceration
17. Unlikely or unwilling to follow-up
18. Nonoperative femoral shaft fracture

#### Inclusion of Children, Women and Members of Minority Groups

We include all individuals who are 18 years of age or greater and skeletally mature. Skeletal maturity is typically achieved by age 18 in males and age 16 in females. We are not including individuals with open growth plates (i.e. skeletally immature patients) because the insertion of rigid intramedullary nails has the potential to damage the growth plate resulting in growth arrest and deformity. We are also collecting information on gender and race/ethnicity in our baseline evaluation forms. A semi-annual report will detail patients (males, females, unknown) enrolled in the study by

the following categories: American Indian or Alaskan Native, Asian or Pacific Islander, Black-not Hispanic origin, White-not Hispanic origin, Other or unknown.

#### Data and Safety Monitoring Plan

(A data and safety monitoring plan describes how the study will be overseen for subject safety and data integrity.)

The Data Safety Monitoring Board (DSMB) will act in an advisory capacity to the Steering Committee (Appendix A) concerning the safety and progress of the study, "Functional Outcomes of Femoral Shaft Fractures: A Multicenter, Prospective Study on Surgery Timing and the Effect on Local and Systemic Complications" conducted under the direction of David C. Teague, M.D., of the University of Oklahoma Health Sciences Center. This study was initiated by a Steering Committee of orthopaedic surgeons and is not funded by any external source. The study is taking place at 20 sites across the United States and Canada.

#### The responsibility of the DSMB is to:

- Review the research protocol, informed consent documents and plans for data safety and monitoring;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants of the ethics of the trial;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of study participants;
- Report on the safety and progress of the trial;

- Make recommendations to the steering committee concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse affects of the treatments under study;
- If appropriate, conduct interim analysis of the efficacy in accordance with stopping rules which are clearly defined in advance of data analysis and have the approval of the DSMB;
- Ensure the confidentiality of the trial data and the results of monitoring; and,
- Assist the Steering Committee by commenting on any problems with the study conduct, enrollment, sample size, and/or data collection.

### Membership

Our Data Safety Monitoring Board consists of two independent Orthopaedic Surgeons who will review data and submit reports twice per year.

- Thomas A. Einhorn, MD - Professor and Chairman, Department of Orthopaedic Surgery Boston University School of Medicine, Boston, MA
- T.A. Russell, MD - Professor of Orthopaedic Surgery, University of Tennessee, Memphis, Tennessee

### Conflicts of Interest

The individuals on the DSMB must disclose any potential conflicts of interest, whether real or perceived, to the PI and steering committee. Conflict of interest can include professional, interest, proprietary interest, and miscellaneous interest as described in 45 CFR Part 94. Potential conflicts which develop during a member's tenure on a DSMB must also be disclosed. Written documentation attesting to absence of conflict of interest is required annually.

### DSMB Reporting

The DSMB will submit reports to the Steering Committee two times per year. Report materials will be prepared by the coordinating office at the University of Oklahoma Health Sciences Center. Materials will be sent to each DSMB member to review. Additional materials may be provided to the DSMB upon request if necessary to fulfill DSMB responsibilities. All study data will be presented in blinded format unless un-blinded data is requested for safety concerns.

### The DSMB will review:

- Patients enrolled, completed, lost to follow-up
- Baseline characteristics of the study population
- Outcomes of subsets of patients and techniques
- Adverse events and serious adverse events
- Any additional data will be made available to the DSMB upon request.

After review of all materials and additional data (if necessary), the DSMB create a report that includes any recommendations, comments, or concerns. Each DSMB member will sign the report and then send it to each member of the steering committee. After review, the steering committee will distribute the DSMB report to each co-investigator site.

### Release of Study Data

Study results must not be disclosed until reviewed and approved by the DSMB

## Confidentiality

All materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality. Each member of the DSMB must sign a statement of confidentiality.

## Appendix A

### *Femoral Outcomes* Steering Committee:

Paul Tornetta, Boston University Medical Center

Dave Teague, University of Oklahoma - HSC

Mo Bhandari, McMaster University

Andy Schmidt, Hennepin County Medical Center

Emil Schemitsch, St. Michaels – Toronto

Chris Pape, University of Pittsburgh Medical Center

Mike Bosse, Charlotte Medical Center

## **F. Literature Cited**

Winqvist RA, Hansen ST Jr, and Clawson DK. Closed intramedullary nailing of femoral fractures. A report of 520 cases. *J. Bone Surg AM* 1984; 66:529-539.

Brumback RJ, Uwagie-Ero S, Lakatos RP, Poka A, Bathon GH, Burgess AR. Intramedullary nailing of femoral shaft fractures. Part II: Fracture-healing with static interlocking fixation. *J. Bone Joint Surg Am* 1988; 212:35-47.

Wolinsky PR, McCarty E, Shyr Y, Johnson K. Reamed intramedullary nailing of the femur: 551 cases. *J. Trauma* 1999; 46:392-399.

Ostrum RF, Agarwal A, Lakatos R, Poka A. Prospective comparison of retrograde and antegrade femoral intramedullary nailing. *J. Orthop Trauma* 2000; 14:496-501.

Ricci WM, Devinney S, Haidukewich G, Herscovici D, Sanders R. Trochanteric nail insertion and the treatment of femoral shaft fractures. *J. Orthop Trauma* 2005; 19:511-517.

Wickstrom J, Corban MS. Intramedullary fixation for fractures of the femoral shaft. A study of complications in 298 operations. *J Trauma* 1967; 7:551-83.

Smith JE. The results of early and delayed internal fixation of fractures of the shaft of the femur. *J. Bone Joint Surg Br* 1964; 46:28-31.

Seibel R, LaDuca J, Hassett JM, et al. Blunt multiple trauma (ISS 36), femur traction and the pulmonary failure septic state. *Ann Surg* 1985; 202:283.

Riska EB, von Bonsdorff H, Hakkinen S, Jaroma H, Kaviluoto O, Paavilainen T. Primary operative fixation of long bone fractures in patients with multiple injuries. *J. Trauma* 1977; 17:111-21.

Johnson KD, Cadambi A, Seibert B. Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: Effect of early operative stabilization of fractures. *J. Trauma* 1985; 25:375

Bone LB, Johnson KD, Weigelt J, Scheinberg R. Early versus delayed stabilization of femoral fractures. A prospective randomized study. *J. Bone Joint Surg Am* 1989; 71:336-40

Reynolds MA, Richardson JD, Spain DA, Seligson D, Wilson MA, Miller FB. Is the timing of fracture fixation important for the patient with multiple trauma? *Ann Surg* 1995; 222:470-8.

Ecke H, Faupel L, Quoika P. Considerations on the time of surgery of femoral fractures. *Unfallchirurgie* 1985; 11:89-93.

Nast-Kolb D, Waydhas C, Jochum M, Spannagl M, Duswald K, Schweiberer L. Is there a favorable time for the management of femoral shaft fractures in polytrauma? *Chirurg* 1990; 61:259-65.

Pape HC, Auf'm Kolk M, Paffrath T, Regel G, Sturm JA, Tscherne H. Primary intramedullary femur fixation in multiple trauma patients with associated lung contusion—a cause of post-traumatic ARDS? *J. Trauma* 1993; 34:540-8.

Pape HC, Regel G, Dwenger A, et al. Influences of different methods of intramedullary femoral nailing on lung function in patients with multiple trauma. *J. Traum* 1993; 35:709-715.

Pape HC, Bund M, Meier R, Piepenbrock S, von Glinski S, Tscherne H. Pulmonary dysfunction following primary bilateral femoral nailing—a case report. *Intensive Care Med* 1999; 25:547.

Pape HC, Schmidt RE, Rice J, et al. Biomechanical changes after trauma and skeletal surgery of the lower extremity: Quantification of the operative burden. *Crit Care Med* 2000; 28:3441-3448.

Scalea TM, Boswell SA, Scott JD, et al. External fixation as a bridge to intramedullary nailing for patients with multiple injuries and femur fractures: Damage control orthopaedics. *J. Trauma* 2000; 48:613-621.

MacKenzie EJ, Bosse MJ, Pollak AN, Webb LX, Swiontkowski MF, Kellam JF, Smith DG, Sanders RW, Jones AL, Starr AJ, McAndrew MP, Patterson BM, Burgess AR, Castillo RC. Long-term persistence of disability following severe lower-limb trauma. Results of a seven-year follow-up. *J. Bone Joint Surg Am* 2005; 87:1801-9.

The SPRINT Study Group. Functional, general, and disability outcomes after tibial nailing: A randomized trial. Unpublished data, submitted for publication.

Ricci WM, Schwappach J, Tucker M, Coupe K, Brandt A, Sanders R, Leighton R. Trochanteric versus piriformis entry portal for the treatment of femoral shaft fractures. *J. Orthop Trauma* 2006; 20:663-667.

Moed BR, Watson JT. Retrograde nailing of the femoral shaft. J. Am Acad of Orthop Surg 1999; 7:209-216

Kain M, Brown D, Tornetta P. Anterograde versus retrograde femoral nailing: A prospective randomized evaluation. Unpublished data.