Title: Evaluation of the Necessity of Operative Irrigation and Debridement: Pediatric Randomized trial of type One Open Fractures (PROOF)

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A. Scientific Aims:

Clinical Trial Portion:

1. Do patients with type one open fractures treated in the emergency department with irrigation have a non-inferior rate of infections compared to those treated in the operating room with formal irrigation and debridement? The response variable will be the presence of an infection in children with open fractures.
2. Do patients with type I open fractures who are treated nonoperatively have a non-inferior time to bone healing when compared to those treated operatively? The response variable will be time to clinical and radiographic fracture healing.

Hypothesis: Minor open fractures in children can be safely treated in the emergency room with irrigation, closed reduction and home antibiotics without an increased risk of infection or a longer time to healing.

a. Null Hypothesis: Open fractures treated in the emergency room will have a higher rate of infection, and a longer time to complete healing.

Survey Portion:

3. What are the current attitudes among members of the Pediatric Orthopaedic Society of North America (POSNA) toward the treatment of type one open fractures in the pediatric population?

Hypothesis: There will be no consensus in the treatment of type 1 open fractures in the pediatric population in regards to whether or not formal irrigation and debridement is necessary, antibiotic use, and timing for fractures.

A. Significance:

Fractures in which bone has been exposed through an associated skin injury, known as open fractures, are frequently encountered in orthopaedics. Open fractures traditionally call for formal operative treatment in which the bone is exposed, foreign tissue is debrided and the wound is irrigated. Open fractures can differ in terms of the bone involved, energy causing the injury and the skeletal maturity of the patient. Children, for example, have a thick periosteum which may decrease healing time and diminish the infection rate due to its robust blood supply. In addition, operative debridement was introduced at the same time as widespread antibiotic use. It is not known whether the mechanical operative management or antibiotic use has resulted in improved outcomes. In retrospective studies, centers are reporting that non-operative treatment may result in comparable outcomes without the time and expense of the operative theater.

The potential advantages of non-operative treatment include shorter hospital stays, avoiding the risk of general anesthesia, lower costs and lack of a larger incision. Still, operative debridement has minimal additional morbidity, so for a child to be treated nonoperatively, the infection rate must not be significantly different from the gold standard operative management. In order to compare these two different treatments, a prospective randomized non-inferiority trial is necessary and warranted. Either patients are going to the operating room when emergency room treatment will be adequate or they are receiving inadequate care when they avoid operating room management.

C. Historical Review:
The management of open fractures is well established in the orthopaedic literature and traditionally calls for prompt initiation of antibiotics and tetanus prophylaxis followed by operative debridement and stabilization. The classification utilized by most orthopaedic surgeons was developed by Gustillo and Anderson and divides open fractures into three types.(1) Type I have a wound smaller than 1cm with minimal soft tissue damage or contamination. Type II open fractures have wounds larger than 1 cm with no extensive soft tissue injury. Type III open fracture has extensive soft tissue damage. Type II and III open fractures continue to be treated with surgical debridement. However, type I open fracture management is controversial since there is a well preserved soft tissue envelope, good vascular supply to the zone of injury, and minimal contamination from the outside world. Children have a thick periosteum which may diminish the rate of infection and decrease the time to healing. It is not known whether the mechanical operative management or antibiotic use has resulted in improved outcomes. The preserved periosteum and soft tissue may allow good antibiotic penetrance to the bone.

In retrospective studies, centers are reporting emergency department management alone may result in equal results without the time and expense of the operative theater. A recent retrospective chart review pilot/feasibility study demonstrated the safe non-operative management of pediatric Type I open fractures.(2) The infection rate was 4% based on observation of 25 patients. In another retrospective review, a 0% infection rate was found among 91 patients (13 were children) who were treated non-operatively for isolated Type I open fractures. (3) A 2.5% infection rate was found another retrospective case review.(4) All of these infection rates compare favorable to operatively treated Type I open fractures from the literature which note anywhere from a 0-7.1% rate. (5-7) However, due to the low rate of infection at baseline as well as due to the relative rarity of the condition, these studies would be underpowered to show a difference. In addition, these studies were retrospective, had multiple types of treatment protocols, and had different definitions of infection. None of these studies noted an incidence of gas gangrene – a rare but devastating historical complication of open fractures. In a literature review, the incidence of gas gangrene, which is thought to be influenced by primary wound closure – a practice with is now commonplace, may not be influenced by methods of irrigation. Authors of such retrospective studies have called for a prospective randomized study to determine if immediate operative treatment of Type I open fractures is necessary to prevent infection.

D. Previous Work:
The protocol, which will be described below, has been in pilot form, approved by the Institutional Review Board, since March 2009. We have approached 16 children for approval into the study. Thirteen (81%) families agreed to the study and were randomized.

Of the two families who did not agree to participate, one refused surgery, despite our recommendation of surgical intervention outside of the study protocol, and was treated with emergency room management, antibiotics and close follow up. This patient healed well without infection or delayed healing. The other two patients' families declined participation and were formally irrigated and debrided in the operating room.

Of the thirteen patients who agreed to participate, six were randomized to emergency room treatment and seven were randomized to operating room treatment. One of the patients, randomized to operating room treatment fracture was NOT found to have an open fracture and

will be eliminated from final formal assessment beyond intent to treat analysis. Another patient who was randomized to the operating room chose not to undergo surgery and instead received ED treatment only. None of the twelve patients' fractures, enrolled in the study, were complicated by infection or delayed healing. There have been no differences in anesthesia/sedation related complications.

E. Methods:

Clinical Trial Portion

Design of the study: A prospective, randomized unblinded non-inferiority clinical trial of children with Type I open fractures to evaluate whether emergency room management and close follow up will not be inferior to formal operative irrigation and debridement in terms of infection rates and bone healing times. The baseline rate of infection with open fractures, treated operatively, is noted to be 0-10% in the literature. We will choose a baseline infection rate of 1%.

Study population:

Inclusion Criteria - Patients will be included if their age is between 3 and 14 years, if the fracture is amenable to treatment by closed reduction, a low energy injury (falls from less than 10 feet, bicycle accidents), wounds less than 1 cm in length and the bone not visualized through the skin.

Exclusion Criteria - Patients will be excluded if they do not meet inclusion criteria, if the fracture would typically require operative reduction and fixation, if their mechanism was high energy (struck by vehicle, motor vehicle accidents, fall from height greater than 10 feet), if there is gross contamination of the wound, or if the open injury involved the hands or feet (the current standard of care to treat open injuries involving hands or feet is only emergency room management).

Study Procedures:

Patients will be recruited from the emergency department at the participating hospitals. All patients with open fractures (fractures associated with a skin wound) who present to emergency department will be assessed for inclusion. The initial assessment of open fracture will be identified by the emergency room physician who will discuss with the attending on call. The orthopaedic attending will determine if this child is amenable to non-operative treatment and would be considered for study inclusion.

All children will be given antibiotics (Ancef 25mg/kg up to 1gm, or clindamycin if allergic to first generation cephalosporin or penicillin) and if the inclusion criteria are met, will be offered to participate in the study by the orthopaedic surgeon or their delegate. If the patient refused study inclusion, they will then be treated per the attending treating physician recommendation.

If the patient agrees to participate he/she will be randomized. The randomization chart is saved in the REDCap database and functions to randomly assign a patient who is entered into the database into a treatment group, stratifying by site. The attending physician will be responsible for determining the randomization assignment by either (1) logging into the REDCap database to enter the patient and randomize them or (2) calling the research coordinator or his/her representative who will then log in to REDCap to randomize the patient. As a backup, the research coordinator will have the randomizations for each site in numbered, sealed envelopes. The study coordinator will be available 24 hours a day to provide the randomization assignment, the consent form (see consent process below), and answer questions prior to treatment arm assignment. Children in both arms of the study will receive emergency room irrigation with one liter of normal saline, realignment/reduction of the fracture, and casting. Conscious sedation will

usually be necessary for this to occur. Patients will be admitted and have up to 24 hours from the time of injury to make a final decision.

No difference in outcomes have been shown in patients with open fractures treated with operative debridement in less than 6 hours compared with those treated from 6 to 24 hours.(8) The surgical timing will be determined by the attending orthopaedic surgeon.

Baseline assessment will include the child's age, mechanism of injury, bone fractured, wound side and location, state of skin injury, whether gross contamination is present, neurovascular status, comorbid conditions.

Additionally, if patients do not wish to be randomized to a treatment arm, they will still be presented with an option for study enrollment. They may take part in a prospective chart review in which the same data will be collected as those patients who were randomized. The data collected at both the baseline and follow-up will match the data collected from patients who randomized to a treatment arm. Patients will consult with their physician regarding treatment for their injury and decide which treatment method they prefer. They will then be consented by the study coordinator or an investigator who will describe the study and the data that will be gathered from their medical charts.

Intervention allocation:
The randomization assignment will be completed and accessible only by the study coordinator. The coordinator will have the assignments in numbered, sealed, radio opaque envelopes in sequential order by the study site. The envelopes will be made by an independent study assistant and determined by block allocation with a 1:1 ratio of operative room vs. emergency room management with permuted, mixed blocks of 4 and 6 created randomly. Randomization will be stratified by each center but by no other factors. The order of these permuted blocks will be determined by random number chart.

Experimental and Control Interventions:
Children will be randomized into two treatment arms – formal operative management (OR) and emergency department (ED) management. Children randomized to the OR arm will be taken to the OR within 24 hours for irrigation and debridement and appropriate bone management. Patients who randomize to non-operative treatment will only be given conscious sedation in the emergency department where the bone will be reduced and casted and the wound will be washed out with one liter of normal saline. All patients will be admitted for 24 hours of intravenous antibiotics post treatment and then sent home with 7 days of oral antibiotics.

Follow up visit description and schedule:
The family will be instructed to look for signs of infection including increased pain, fevers, or odor coming from the cast. All patients will follow up 5-7 days after the injury where the cast will be windowed and the wound examined. This follow-up appointment is standard of care for all Type I open fractures. Infection will be defined as the Surgical Site Infection by the CDC (see Supplementary information section) guidelines. Signs of infection such as erythema and wound drainage will be treated at the discretion of the attending orthopaedic surgeon with additional antibiotics, local wound care, or formal operative debridement. If no signs of infection are noted then the cast will be repaired. Radiographs will be obtained, as is the standard of care, at all follow up visits. Future follow up visits will not include a routine wound examination unless clinically indicated – fevers, increasing pain, foul odor from cast, etc.

Follow up appointments will be standard of care (non-research related) and will be at approximately 1, 2, 4, 6, 12 and 24 weeks post op.

Informed Consent Process:
If the patient agrees to participate he/she will be formally consented and randomized by calling the study coordinator. The study coordinator, or a representative, will be available 24 hours/day to provide the Parent Permission (consent) form, Adolescent Assent form, and HIPAA Authorization form (if separate from the consent form). At each institution, each participant will be consented using the IRB approved consent and assent forms and HIPAA Authorizations of their institution. The study coordinator, or representative, will have digital copies of each participating institutions' consent forms, assent forms, and HIPAA Authorizations in order to obtain consent remotely at that institution. The study coordinator, or representative, obtaining consent will be listed on the authorized personnel list of the institution that joins the study and has IRB approval to obtain consent with this electronic, remote procedure.

Each institution that agrees to remotely consent participants, will be provided with a tablet (such as an iPad mini tablet) for obtaining consent and HIPAA Authorization for participation in the study by the primary institution. The study coordinator from the primary institution (Ann & Robert H. Lurie Children's Hospital of Chicago) will use the tablet and the designated applications to discuss the study with the patient via electronic communication (for example, by using the "FaceTime" application, Skype, etc. The study coordinator will first present an introduction / information sheet that will explain how the consent process will take place and what information will be requested of the participant prior to signing the consent form. The introduction/information sheet will also explain that the transmission of the consent process is being done electronically, through the use of third party providers, and will disclose what information may or may not be saved by these third parties. The study coordinator will then seek verbal consent to proceed with the consent process after this introduction/information sheet has been read. The study coordinator will provide the consent/assent forms and HIPAA Authorization, and answer questions prior to treatment arm assignment. The consent process will be performed in a private room to maintain participant privacy.

The study coordinator will be able to consent the patient through the SignNow application on the tablet. This application will allow participants to access copies of the consent/assent forms and HIPAA Authorizations digitally and at the same time talk with the study coordinator about the forms. This allows the study coordinator to complete a full, interactive, consent process with the potential participant. Participants will be able to ask the study coordinator all questions via the tablet and the study coordinator will be able to provide answers in "real-time." If the parent/child agrees to participate in the study, the parent/legally authorized representative will sign the consent and HIPAA Authorization with a digital signature, that can be witnessed in "real-time" by the study coordinator obtaining consent. In addition, the study coordinator can then co-sign the consent and HIPAA Authorization as the person obtaining consent.

After obtaining parent/legally authorized representative permission for the child to participate in the study, the study coordinator will then obtain assent from the child. Written assent will be obtained according to each participating institutions' guidelines. At Lurie Children's this will be for all participants ages 12-17 years of age. In addition, verbal assent will be obtained from younger patients that is both age and developmentally appropriate. Steps will be taken by the study coordinator to minimize undue influence and coercion.

Copies of signed consent forms will be sent to the patient and their family primarily via email. The study coordinator can send these copies to the family immediately after they have been signed. If the family prefers to have hard copies of these signed documents, the study coordinator can print and mail the documents to their home. PIs will be sent electronic copies of the study documents to sign and will save these documents in a password-protected folder on a secure server.

If a patient or their family requests to discuss the study with a treating physician in person they will be given the opportunity to do so. If the patient or their family decide that they do not want to be enrolled in the study remotely, they may refuse this option. In this case, the patient will not be enrolled unless a member of the study team is able to meet with the patient and conduct the consent process in person.

Hard copies of the consent and assent forms will also be made available as back up. Each participating site will also have the option of completing the consenting process in person with paper copies of the consent form, if staffing and time allows. Hard copies of these consent forms can be stored in the office of the research coordinator or within the hospital's emergency department and/or OR, per site preference. If patients sign hard copies of the consent and assent forms, these hard copies will be given to the PI and stored in a locked cabinet in his/her office.

Consent and assent documents will be translated into Spanish to include the enrollment of Spanish-speaking families on a site-by-site basis depending on the local patient population. The consent process for all Spanish-speaking families can be completely remotely via the tablet when there is in an in-person translator available at the site of recruitment. If a given site does not have an in-person translator, the member of the study team at Lurie Children's cannot remotely consent the patient. Hard copies of these translated forms will be kept in either the research coordinator's office or on-site at the hospital. After consent is fully executed, patients will receive their randomization assignment and will be provided with further instructions on proceeding with their assigned treatment.

Consent and Enrollment Documentation:
When the study coordinator at Lurie Children's consents patients remotely, they will document the date and time of consent and the name of the institution at which the patient is receiving treatment. This information will be stored in a database on a password-protected computer along with the electronic copies of the signed consent documents. The research coordinator at Lurie Children's will email electronic copies of the signed consent forms to the research coordinator at the site from which the patient was recruited. The research coordinators at each participating site will be responsible for ensuring that the consent documents are filed with the patient's medical record according to site-specific requirements.

Research coordinators at other sites will be asked to send a monthly log to the research coordinator at Lurie Children's recording their recruitment process. Information recorded on this log will include the total number of patients approached for recruitment, the number enrolled, their treatment randomizations and whether they were consented by study investigators in person or remotely. The number of patients who did not meet inclusion criteria or who declined enrollment, as well as their reasons for declining, will also be recorded. The research coordinator at Lurie Children's will be in touch with the research coordinator at each site to ensure this monthly log is accurately completed. The local research coordinator will be responsible for keeping a database of the consent information for all patients enrolled at their site (whether they were consented in person or remotely). In the event that a site does not have research staff, the

research coordinator at Lurie Children's will be in communication with the PI on a monthly basis and will complete this recruitment log for them.

Tablet Setup and Use:
Prior to being distributed among the sites, tablets will be set up with the applications necessary to the consent process. Instructions regarding the use of these applications will be given to each site. The tablet at each site will have the required consent documents saved and easily accessible within the SignNow application. Use of the FaceTime application will require the research coordinator (or another investigator) to create an Apple ID that can be used as the general login for that site. The number for the research coordinator at Lurie Children's will be pre-programmed into the tablet.

The attending physician or other clinical and/or research staff will help the patient make the initial call to the study coordinator at Lurie Children's. Once the connection has been established, the study coordinator will be able to direct the patient through the process of electronically signing the consent form. If the patient has any technical difficulty with the tablet they can ask the local investigators for assistance. If there are problems with the FaceTime connection, a patient cannot be enrolled unless a local investigator is able to complete the consent process in person. If there are problems with the SignNow application, the patient and their parent can sign the hard copies of the local consent documents that will be on file with the site's research coordinator or stored within the hospital.

Applications:

SignNow: The SignNow application is utilized for the purposes of obtaining electronic signatures on documents. Template documents can be uploaded so that the same document can be used to obtain signatures multiple times. Once a template is signed, the signed copy of the document is automatically saved to the "Documents" folder on the application. This application also allows for the study coordinator or investigator to email documents to other personnel in order to request signatures on the form; such as a co-signature from a PI if it is required by the study site.

All consent and assent documents required by a given site will be uploaded onto the SignNow application on that site's personal tablet. All sites are required to submit current and approved copies of their consent documents to the main study site, Lurie Children's. Prior to sending the tablet to a site, the research coordinator at Lurie Children's will upload the site's consent and assent documents as templates into the SignNow application. Upon periodic review, or if there are changes made to the consent forms, each site will be required to send the most recent, approved version of the consent to the research coordinator at Lurie Children's to upload into the SignNow application. The SignNow application will be accessed using a login that is central to all sites. This login information will be saved on the tablet and the login credentials will also be given out to each site.

When a patient is being enrolled they can open up the correct template documents and once they sign them these documents will automatically be saved in a separate folder within the application. Once all of the necessary signatures have been obtained from the participant or their parent, the person obtaining consent and the PI (if required by study site), the document will be saved into a consent folder on the password-protected computer of the local PI. At this point, the consent and assent documents can be deleted from the tablet application. This protocol for saving documents will help to prevent any breach in confidentiality by removing the consent documents

from the portable tablets and storing them on protected servers. As stated in the Terms of Use, the SignNow application will collect and store files used within SignNow until they are deleted from the tablet and saved onto the password-protected computer of the local PI. The SignNow application will also be able to access uploaded file information (including file extensions, sizes, thumbnails, modified dates, etc.) for the purpose of providing system maintenance, management, and technical support.

The personal information that may be accessed by SignNow is only that of the research coordinator who establishes the login credentials for the project across all sites involved. No personal information of patients will be stored by or available to the Barracuda Networks, Inc who own the SignNow application.

FaceTime: The FaceTime application allows for both video and audio calls between iPhones, iPads, Macs and the iPod Touch through either an internet or cellular connection. FaceTime uses a digital camera on the devices that faces the user and allows for video calls to be made between two individuals. Both the caller and the receiver can see each other, as well as a smaller video image of themselves.

For the purposes of this study, the video feature will be used for the research coordinator at the lead site to remotely consent patients at other locations. Use of this application for the consent process will only be used at approved sites. This application allows the tablet at one site to call the tablet at the main site through the wireless internet connection. The research coordinator at a given site will create an Apple ID specifically for use on their tablet to login to FaceTime. Patients will not be required to provide an Apple ID or any other sort of personal information in order to use this application. Therefore, no private information of the patient will be saved within the FaceTime application. In agreeing to the use of the tablet for the consent process, participants will be agreeing to the terms of use for the FaceTime application. The patient and/or their parent also have the option to refuse consent via the tablet, in which case a local investigator must consent the patient in person. Additionally, if there are problems with the application or internet connection used to make the call, a study investigator must alternatively consent the patient in person in order for them to be enrolled in the study.

Data Analysis

Ascertainment of response variables:
(Specific Aim 1) An infection will be considered if a return visit to the operating room is necessary for wound complication post randomization and intravenous antibiotics or if the attending surgeon feels that additional antibiotics are necessary, at any time, after the initial seven day course.

(Specific Aim 2) Union of the fracture will be determined by radiographic parameters of callous being on three of four sides of bone without tenderness to palpation. The radiographs will be read by the attending orthopaedic surgeon at each clinic visit to determine treatment. Loss of reduction will be noted but will not be considered a complication since it can occur whether or not operative debridement was performed. A revision reduction can be performed at the attending orthopaedic surgeon's discretion. In the final analysis phase, an orthopaedic surgeon, blinded to the treatment, at Lurie Children's will be utilized to review all of the patient's radiographs to determine bridging callous on three sides of the bone. This reviewer will be blinded to the patient's name, treatment group but will have access to the length of time since the fracture occurred. Additional procedures or deviations from the protocol will be noted. We will

also carefully examine the rates of anesthesia and sedation related complications including nausea and vomiting, respiratory depression, aspiration, hoarseness, and emergence agitation.

Sample size assumptions and estimates:
This will be a non-inferiority trial as we attempt to demonstrate that ED management is not inferior to OR management.

For the binary outcome of infection (**Specific Aim 1**), we estimate an infection rate of 1% in the reference (OR) group since the literature notes an infection rate between 0% and 5%. Based on a survey of pediatric orthopedic surgeons, an acceptable margin of non-inferiority can be estimated at approximately 4% (i.e., accept a 5% infection rate in the ED group), as the survey suggests surgeons will accept a 5% infection rate in order to avoid formal operative treatment of children with open fractures. We will test the following hypotheses: H_0: P_T-$P_C \geq \Delta$ vs. H_1: P_T-$P_C < \Delta$. In order to test these hypotheses in a non-inferiority design at the one-sided 2.5% level of significance, we will construct a two-sided 95% confidence interval for the difference in proportion of infections (P_T-P_C) across the two groups. If the upper confidence limit is less than our acceptable margin of non-inferiority (Δ=4%), then we would conclude ED management is not inferior to OR management with respect to infection rates.

The following are power estimates based on 10000 simulations under the above conditions for various feasible sample sizes. We also obtained power estimates for the scenario involving a 2% infection rate in the control group (OD).

Sample size/arm	Reference Proportion	Power (Δ=0.03)	Power (Δ=0.04)	Power (Δ=0.05)	Power (Δ=0.06)
70	0.01	0.5091	0.6766	0.8536	0.866
80	0.01	0.5164	0.8107	0.8382	0.9434
90	0.01	0.4865	0.786	0.8734	0.9489
100	0.01	0.7416	0.7878	0.9254	0.9616
110	0.01	0.6994	0.8383	0.9245	0.976
120	0.01	0.6926	0.894	0.9437	0.9763
130	0.01	0.714	0.8738	0.9621	0.981
140	0.01	0.6907	0.8783	0.9624	0.99
150	0.01	0.7606	**0.9111**	0.9748	0.9928
160	0.01	0.8221	0.9394	0.9816	0.997
170	0.01	0.795	0.9427	0.9842	0.998
180	0.01	0.821	0.9339	0.9876	0.9984
190	0.01	0.8147	0.9573	0.9936	0.9987
200	0.01	0.848	0.9629	0.9928	0.9987
210	0.01	0.8503	0.9669	0.9941	0.9995
220	0.01	0.8675	0.9743	0.9961	0.9992
130	0.02	0.4748	0.6378	0.8123	0.9066
140	0.02	0.4906	0.6922	0.8385	0.9288
150	0.02	0.5051	0.7048	0.8785	0.9466
160	0.02	0.5642	0.7452	0.8678	0.9593

170	0.02	0.5458	0.7621	0.8958	0.9679
180	0.02	0.5651	0.7737	0.9165	0.9682
190	0.02	0.5864	0.8088	0.9317	0.9733
200	0.02	0.5865	0.8005	0.9275	0.9807
210	0.02	0.6349	0.8346	0.943	0.9833
220	0.02	0.61	0.842	0.9504	0.9868

For outcome of healing time **(Specific Aim 2),** most fractures have a healing time of 6 weeks with an estimated standard deviation of 1 week. We will again try to show ED management is not inferior with respect to healing time when compared to OR management, assuming a margin of non-inferiority of one week (Δ=1). Assuming a one-sided 0.025 level of significance and power (1-β) equal to 0.90, the number of subjects required per treatment group can be calculated as follows:

H_0: $\mu_C-\mu_T \geq \Delta$ vs. H_1: $\mu_C-\mu_T < \Delta$

$$N = \frac{2(Z_\alpha+Z_{1-\beta})^2\sigma^2}{\Delta^2}$$

$$N = \frac{2(1.96+1.282)^2 1^2}{1^2} \qquad N = 21$$

Our results suggest that a **sample size of 150 per group (300 total)** would provide 91% power to detect non-inferiority of emergency room management when compared to operating room treatment in the type one open fractures under the assumptions outlined above. We have accepted a 5% infection rate (4% shift from the hypothesized reference rate). If the baseline infection rate is 2%, this study would be adequately powered (87%) to show non-inferiority for a margin of 5% (7% infection rate in the ED arm). As the calculation above illustrates, the study is also well powered to demonstrate non-inferiority with respect to healing time.

Site estimates:

The following sites have provided the initial estimates as to how many patients they feel could be enrolled in a given year: Lurie Children's = 2/year, Vancouver Children's Hospital 5/y, Riley Children's= 2/y, University of Mississippi Medical Center = 9/y, Mary Bridge Children's Hospital= 12/y, Yale-New Haven Children's Hospital= 4/y, Carrie Tingley Children's Hospital= 20/y, Phoenix Children's Hospital= 20/y, Nationwide Children's Hospital= 20y, IWK Health Centre, Halifax=4/y, Denver Children's Hospital=12/y. Texas Children's Hospital= 12/y, Morristown Medical Center = 2/y, New York University Medical Center = 4/y. Approximate Total= 128/y.

Subject Recruitment:

The number of subjects needed for this trial is large. To date, the pilot study has had an excellent recruitment (80% see below) rate, so we expect similar rates at participating centers. Currently, with the 14 sites who have agreed to participate thus far, the expected recruitment is 128 patients per year. We plan to add 4-6 more sites during the Planning Grant Period which would expand the projected total recruitment to 160 patients per year. Therefore, when the study is at full capacity, we conservatively anticipate recruiting 120 patients per year (assuming 75% recruitment rate) over the 3 year grant period, for a total of 360 patients, which surpasses the calculated 300 patients needed for adequate statistical power. We are accepting and powering for a 5% infection rate in the ED arm. If we were to accept a 6% infection rate (i.e., a 5% margin of non-inferiority) then we would require only 190 patients. For a 7% infection rate (Δ=0.06), we will need 150 patients. If recruitment is lower than expected, we could accept a larger

margin of non-inferiority given the large range of type I open fracture rate (0-10%) in the literature.

If we are only able to recruit 150 patients, and the rates of infection in the OR and ED groups are nearly equal, we will consider halting the study and releasing the results. This will be decided by the Steering Committee in conjunction with the funding agency. Alternatively, the Steering Committee could decide to prolong the study to achieve increased numbers for the comparison.

Data management:
An initial hard copy survey of the initial data will be completed by the attending surgeon with the study coordinator's assistance. Data collected will include name, MRN, telephone number, age, injury mechanism, bone fractured, wound size (in cm), wound location, state of skin, neurovascular status, comorbid conditions, antibiotics given, tetanus status, surgical procedure description and anesthesia/sedation complications. At the 1-week follow up visit, a survey will be completed by the attending surgeon which will ask if fevers are/have been present, wound drainage through cast, skin and wound examination (erythema, drainage), whether additional antibiotics are necessary, and the reduction of the bone on radiographs. The survey completed by the treating orthopaedic surgeon at subsequent visits will also ask if fevers are presents, if pain has increased, wound drainage, if a second look at the wound was necessary, reduction of the fracture, and healing.

An online database has been created using REDCap technology. Name, MRN and telephone number will be recorded in site-specific Excel files. Non-identifying data will be recorded in REDCap. Information from the initial and follow up visits will be entered into the databases by the surgeon or his representative which will be password protected. Each patient will have a unique identifier. Randomization allocation can also be found through the REDCap site.

Data Analysis:
We will use an independent two-sample confidence interval for binomial proportions comparing infection rates between the two treatment arms. If the upper limit of a two-sided, 95% confidence interval is less than the margin of non-inferiority, we will have evidence that ED management is not inferior to OR management. Similarly, an independent two-sample confidence for difference in mean healing time will be constructed and used in the same manner to determine evidence of non-inferiority. Both large sample, normal approximation methods and exact methods will be explored. Descriptive data will be used to relay anesthesia complications, additional procedures and significant infections. Primary analysis will be based on the "as treated" principle, and an intent-to-treat analysis will also be conducted. We expect almost no cross-over in the initial 24 hours after injury. We will also use Kaplan-Meier estimation to create curves comparing cumulative incidence of infection as well as time to healing for the duration of study follow-up.

Data Security:

Research Electronic Data Capture (REDCap)
REDCap is a secure application used for managing online databases for collecting research data. The software allows data to be stored over a secure web connection with authentication and data logging features. The database creates a log of all activity including information such as the date, time and user who performed the action. The database is password protected and only approved users are able to access projects through REDCap. Data for all sites involved in this multi-center project will be stored in this electronic database. PIs and research coordinators from each site

will be assigned Northwestern University Affiliate NetIDs which will give them access to REDCap through Northwestern University Clinical and Translational Sciences Institute (NUCATS). Once these NetIDs are granted, the research coordinator at Lurie Children's will then add these individuals to the REDCap project.

Within the open fracture database, Data Access Groups have been established for each site. Data Access Groups allow each site access only to the data from patients that have been enrolled at their institution. Once NetIDs have been established for each PI and research coordinator, the research coordinator at Lurie Children's will designate those individuals to the appropriate data access group. The research coordinator at Lurie Children's will also set user rights for individuals from other institutions. These user rights will include adding/editing data reports within their Data Access Group and randomizing patients. Data will be de-identified when entered into REDCap and the research coordinator at each site will be responsible for maintaining a spreadsheet linking research identification numbers to the names of the patients. Each research identification number will be unique and un-identifiable.

Each site will assign a unique identifier as they enroll and randomize a patient into the study. The identifier will include the name of their site, followed by a sequential, three digit number (E.g., Lurie-001, Lurie-002) in order to ensure numbers are not duplicated. Additionally, REDCap will assign a sequential ID number to each patient across all sites as they enroll in this study.

Tablets

The research coordinator at Lurie Children's will purchase the tablets for all other sites involved and will ensure that they are encrypted. The research coordinator will communicate with the research coordinator or PI at each site in order to establish a common Apple ID that can be used for the site. The Apple IDs/passwords for each site will be stored in a database at the main study site. The research coordinator will then download all of the applications necessary to the recruitment process. The SignNow application will be set up using the login credentials central to all sites involved with this project and the coordinator will ensure all necessary consent/assent/HIPAA documents for that specific site are available within the application. The research coordinator will also create a unique 4-digit passcode for each site to lock the tablet.

Once the tablets are completely set up, they will be shipped to the various sites and each site will be given the passcode to unlock the tablet. Research coordinators at each site will be responsible for the maintenance and usage of the tablets. Tablets should be restricted to areas of the hospital in which they will be used to recruit patients. It will be required that the tablets be kept in locked cabinets when not in use for the consent process. In order to prevent the loss of the tablets, the research coordinator at a given site should use a check-out sheet for research assistants and other personnel involved in this project to keep track of who has the tablet at any given time. As the tablets at other sites will be used solely for the purposes of consenting patients, they should remain in the hospital and should not be taken home by any individual for personal use. All tablets will also be given a location app so that stolen tablets can be found. All tablets will also have a label on them instructing that if found – whom to contact at both the local and national site.

The tablets will be set up with restrictions so that the ability to install other applications is disabled. While these restrictive settings can technically be undone by local study team members who know the Apple ID credentials, it will be the responsibility of the research coordinator at each site to monitor the use of the iPads and ensure that they are not used for purposes outside of this study.

Before and after each patient is consented, the tablet should be wiped down using disinfecting wipes in order to prevent the spread of bacteria among patients and staff.

If a tablet is lost or stolen, the research coordinator at the given site should immediately contact the research coordinator at Lurie Children's. At this point, plans will be arranged between the two sites to obtain a new tablet. All tablets will also be given a location app so that stolen tablets can be found. All tablets will also have a label on them instructing that if found – whom to contact at both the local and national site.

Interim monitoring:
The following scale will be used in grading severity of adverse events noted during the study:

Mild adverse event: An infection resulting in continued antibiotic use or a return visit to the Emergency Department. Normal healing without further intervention.
Moderate adverse event: An infection resulting in a return visit to the Emergency Department with the potential for functional difficulties. Return to operating room for debridement.
Severe: A necrotizing infection with the potential for functional difficulties. Multiple debridements necessary in the operating room.

Due to the presumed low infections rates (0-10%), all infection events will be identified and discussed. If any adverse events occur the research coordinator and/or PI at that site will be required to report the event to the PI at Lurie Children's. The PI will discuss any adverse events at bi-monthly phone conferences with the Executive Committee. Such cases will also be discussed amongst the Steering Committee and other site leaders during planned quarterly phone conferences. A formal review by the PI and Site Leaders will be made after the first 40 patients are recruited to see if the infection rate in the non-operative treatment group is above 10%.

If an infection is present, the Principle Investigator and Site Leaders from the various other locations, will discuss the case including the characteristics of the infection, bacteria found, implications of this infection, whether any deviation from the protocol may have been present.

Final analysis:
Statistical differences in the rate of infection and time to healing will be compared between the operatively and emergency room treated groups. Confidence intervals will be determined for the rate of infection, the time to healing and number of additional procedures needed. Kaplan-Meier curves will be created for comparison.

Termination policy:
If during the course of the study, the infection rate in the emergency room treated group is greater than 10% (after a minimum of 40 nonoperatively treated patients) the study will be terminated.

Organization

Participating Investigators:
The central study center will be Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's). It is there that the Principal Investigator and Study Coordinator will be located. The pilot study has taken place at this location. Four additional sites will be included in the Phase 2 of the study. Each of these sites will have a Site Leader (SL) and supported by in house study

personnel. The five sites will be utilized to insure that the recruitment operation, site randomization, and organizational procedures are in place. All data will be run through, housed and analyzed at Lurie Children's. Finally, eight to ten additional sites, (locations to be determined) will be recruited, for a total of 13 -15 sites, each with their own Site Leader to complete the recruitment and treatment of patients.

Study Administration:

Executive committee: This will be made up of the Primary Investigator, Site Leaders from the 5 sites indicated above, and one volunteer from an external site not directly enrolling in the study. They will be in charge reviewing protocol deviations, counseling on study issues, and noting complications. They will meet monthly.

Steering committee – This will be made up of the Primary Investigator and all Site Leaders. They will be in charge of overall organization and will determine if an unsatisfactory rate of infection (>10%) is found.

Funding organization – Funding for the study will be attempted after phase 2 has been completed through NIH and the Pediatric Orthopaedic Society of North America. Funding will be needed for study coordinators and administrative needs. Phase 3 funding will be attempted through NIH and the Orthopaedic Research Education Fund.

Ethical issues:

The main ethical issue associated with this research would be if there is an increased infection rate with children who are randomized to the non-operative arm. These children may require longer term antibiotics or additional surgery. However, if a single surgery is ultimately necessary, the patient may only have lost minor healing time since a surgery was saved initially. Due to the fact that there are now three case series reporting children treated nonoperatively for minor open fracture, multiple centers are using it as their standard treatment practice. While these retrospective studies do not demonstrate an increased infection rate, these case series were all underpowered to show a significant difference. In our survey to POSNA membership, 31% of respondents chose emergency room treatment while 69% chose an operative strategy in the treatment of type I open forearm fracture. Therefore, equipoise exists for this question. The main benefit of this study will be to future children with open fractures. The children in the study will benefit if they were randomized to the ED group and the data shows no signs of infection and a normal healing time because they will have avoided a trip to the operating room.

Risks to Participants:

Patients with Type I open fractures are generally at minimal risk of problems if treated appropriately. The fracture should be treated within 24 hours of the injury to avoid infection. Infections may be caused by bacteria that contaminate the wound at the time of injury. Infections are unusual with this injury and can occur whether the child is taken to surgery. Infection may result in slow healing of the fracture and chronic bone infection. All children with fractures may also experience injury to the nerves or arteries or excessive swelling which can cause injury to muscle tissue. Risks of anesthesia in the Emergency Department or operating room may include breathing problems but are very rare in a previously healthy person. Participants who undergo surgery will be told of the risks related to anesthesia and surgery at that time and will sign a separate, treatment consent for the surgery and anesthesia. Risks of fracture treatment may include alignment problems or poor bone healing. Unknown risks may be involved with this research study.

Benefits:

The main benefit will be to future children with open fractures. The children in this study may benefit if they are randomized to the non-operative group and show no signs of infection with normal healing time. They will have been saved a trip to the operating room.

Survey Portion:
The practices and opinions toward type 1 open fractures in children will have been surveyed at the POSNA 2012 meeting as well as through a web based system (http://www.surveymonkey.com/) that will be distributed to all active members of POSNA after approval by the Evidence Based Medicine Committee. Approximately 600 members will be at the 2012 POSNA meeting. Those who complete the survey at the meeting and turn in their response will be entered into a raffle drawing for a $500 Apple gift certificate. The raffle will take place at the end of the meeting. The odds of winning are 1:600. Additional POSNA members will be captured through the web-based survey which will be available after the meeting distribution. There is no incentive and/or raffle drawing for those who participate in the web based survey option after the meeting.

The questions can be reviewed as part of the supplementary data section. We believe that practice patterns vary significantly and that there will be no consensus opinion toward the treatment of type 1 open fractures in the pediatric population. This survey will provide the documentation of equipoise necessary to apply for additional funding as during phase 3 of the trial.

Subjects: The target population for this project is the entire membership of POSNA.

Survey Instrument:
We have developed 21 close-ended questions to study the attitudes and practices of the target audience along with their demographic information. We have pre tested the questionnaire by asking colleagues (Pediatric orthopedic surgeons within our practice, orthopedic residents) for feedback regarding the survey instrument. The survey will be sent out as a POSNA attachment on three separate occasions in order to obtain the highest percentage of responses. There will also be a question identifying if respondents are interested in participating in this study during Phase 3.

Statistics and Power Analysis
We plan to generate summary descriptive statistics for responses to all survey items, using means and standard deviations for continuous variables and median and interquartile range values for ordinal variables. Point estimates for responses to nominal variables will be generated along with 95% Confidence Intervals on the estimates. Statistical testing will be performed to examine the differences in responses among members based on where they practice, whether they are within an academic center or private practice, and duration of practice time.

F: References:
1. Gustillo RB. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. JBJS AM 1976;58:453-8.
2. Doak, J Pediatr Orthop 2009;29:49-51
3. Yang EC, Eisler J. Treatment of isolated type I open fractures: is emergent operative debridement necessary? Clin Orthop Related Res. 2003;410:289-94.
4. Iobst, CA, et al. Nonoperative management of pediatric type I open fractures. JPO 2005;25:513-7.

5. Grimard, et al. Open fractures of the tibia in children. Clinical Orthopaedics 1996; 332: 62-70.
6. Haasbeck, et al. Open fractures of the arm in children. JBJS Br 1995; 77: 576-81.
7. Skaggs, et al. The effect of delay of surgical treatment on rate of infection of open fractures in children. JPO 2000; 20: 19-22.
8. Skaggs DL, et al. The effect of surgical delay on acute infection following 554 open fractures in children. JBJS Am 2005;87:8-12.

G. Supplementary Information
Pilot Study: See Section D Previous Work

Survey: See Survey attached under separate File

Surgical Site Infection: from Center for Disease Control:
www.cdc.gov/ncidod/dhqp/pdf/nnis/nosinfdefinitions.pdf
Infection occurs within 30 days of surgery
and
involves only skin or subcutaneous tissue
and
patient has at least one of the following

a. purulent drainage from superficial incision
b. organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
c. at least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.
d. diagnosis of superficial incisional SSI by the surgeon or attending physician.

Time Line: See below

CLINICAL TRIAL PLANNING GRANT APPLICATION
Evaluation of the Necessity of Operative Irrigation and Debridement: Pediatric Randomized trial of type One Open Fractures (PROOF)
Joseph A. Janicki, M.D.

Detailed Project Timeline:

Phase 1 (Pilot phase) :

1. *Mar 2009: pilot (1 center) IRB acceptance Lurie Children's Hospital of Chicago – pilot site*
2. *May 2009: pilot (1 center) recruitment begins*
3. *March 2011: Creation and testing of Survey of attitudes of POSNA membership*
4. *September 2011: Submission of Survey to Evidence Based Medicine Committee*
5. *May 2012: Survey presented to POSNA membership of attitudes*
6. *May 2012: POSNA Clinical Trials Award received*
7. *May 2013: Presentation of POSNA membership attitudes from Survey*
8. *November 2013: Completion of Manuscript of POSNA membership attitudes from Survey*

Phase 2 (Small Multicenter Phase)

9. *November 2011 – April 2012: Recruitment of 3 additional sites (Vancouver Children's Hospital, University of Mississippi Children's Hospital, Riley Children's Hospital)*
10. *May 2012: Investigator's Meeting (POSNA Annual Meeting)*
11. *September 2012: Submission of OREF Clinical Trials Grant*
12. *May 2013: POSNA recruitment meeting for additional sites – attended by 20 centers*
13. *June 2013-September 2013: 7 additional sites agree to join trial (total = 11)*
14. *September 2013: Resubmission of OREF Clinical Trials Grant*
15. *March 2013-January 2014: IRB Submission and Approval (1st 5 secondary sites – Riley Children's, Vancouver Children's, Mississippi Children's, Phoenix Children's, IWK Health Center)*
16. *October 2013: Development of the Manual of Operations*
17. *October 2013: phone conference meeting with centers*
18. *September 2013-November 2013: Data Management System – REDCAP creation*
19. *January 2014: Patient Accrual Begins at 5 sites*
20. *Spring 2014: Interim Analysis. Administrative issues to be discussed with enrollment of patients at various centers and data administration and organization at central center. Improvements to be considered and made. Apply for funding from outside organizations.*

Phase 3 (Large Multicenter Trial Phase):

1. *Sept 2013 – May 2014: IRB Submission and approval at new Phase 3 sites (Mary Bridge Children's Hospital, Yale-New Haven Children's Hospital, Carrie Tingley Children's Hospital, Nationwide Children's Hospital, Denver Children's Hospital).*
2. *Oct 2013- May 2014: Recruitment of final 4 sites*
3. *January 2014: Application for NIH R21 grant if necessary*
4. *May 2014: Award of OREF grant*
5. *April 2014: Investigator's Meeting (POSNA Annual Meeting)*
6. *Spring 2014: Patient Accrual Begins at Phase 3 sites*
7. *Winter 2014: Interim Analysis. Administrative issues to be discussed with enrollment of patients at various centers and data administration and organization at central center. Improvements to be considered and made. Apply for funding from outside organizations.*
8. *April 2014: Investigator Meeting (POSNA Annual Meeting)*
9. *August 2016: Patient Accrual Ends*
10. *December 2016: Follow-up Period End (6 months follow-up)*
11. *January 2017: Data Analysis*
12. *January – April 2017: Manuscript Preparation*

H. Animal Studies: not applicable

I. Human Studies:
The Clinical Trial portion of this study has been approved in pilot form by the Institutional Review Board of Ann & Robert H. Lurie Children's Hospital of Chicago 2009 with a renewal February 2013. IRB#2012-13763

We will submit the Survey Portion of this study for IRB approval once the questions have been tested and finalized among a test group of orthopaedic surgeons.

J. Role of Orthopaedic Surgeon:
The orthopaedic surgeon, a candidate member of POSNA, is the principle investigator for this study. He will be responsible for study hypothesis, study design, study funding, corresponding center recruitment, data maintenance, data interpretation, and publishing the manuscript. Orthopaedic surgeons will be site leaders at all of the additional sites and be responsible for facilitating data collection. All site leaders will be involved in the refinement of study methodology, data analysis, and manuscript preparation.

K. Relevance to Pediatric Orthopaedic Society of North America:
The Pediatric Orthopaedic Society of North America works to provide high quality education for pediatric orthopaedists and to provide the best possible patient care. Fracture management, both closed and open, is extremely common in pediatric orthopaedic surgery. Open fracture management is controversial. The standard of care with open fractures may diverge from clinical practice. If this is the case, either patients are going to the operating room when emergency room treatment will be adequate or they are receiving inadequate care when they avoid operating room management. A clinical trial offers the best evidence to answer this question. Moreover, a fundamental mission of POSNA is to support research that improves the care of pediatric orthopaedic conditions. POSNA has been supportive in creating evidence-based medicine through advocating multicenter prospective studies such as the topic of this proposal

APPENDIX

Participating Institutions:

Lurie Children's Hospital
Riley Children Hospital (Indiana)
BC Children's Hospital (Vancouver)
University of Mississippi Medical Center (Batson)
Mary Bridge Children's Hospital (Tacoma, WA)
Yale-New Haven Children's Hospital
Carrie Tingley Children's Hospital (New Mexico)
IWK Health Center (Halifax)
Phoenix Children's Hospital
Texas's Childrens Hospital
Children's Hospital Colorado
Nationwide Children's Hospital (Columbus, OH)
Morristown Medical Center (New Jersey)
NYUMC-Hospital for Joint Diseases
Children's Medical Center Dallas
Carolinas Healthcare System
Children's Hospital Los Angeles (CHLA)
Orthopaedic Institute for Children (UCLA)
Children's Hospital at Montefiore (Bronx, NY)
Johns Hopkins (Baltimore, MD)