SYSTEMATIC REVIEW AND META-ANALYSIS OF CLINICAL OUTCOMES OF FRACTURES FIXED WITH THE SURGICAL IMPLANT GENERATION NETWORK (SIGN) INTRAMEDULLARY NAIL

A thesis submitted to the University of Arizona College of Medicine – Phoenix in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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**Introduction:** The (Surgical Implant Generation Network) SIGN Intramedullary (IM) nail is designed to fix long bone fractures without using a costly C-arm imaging device. It is distributed for free to countries in need, allowing for elevation of care from the standard, lengthy traction treatment in those countries to clinically superior IM nailing. This paper compares the clinical outcomes of the SIGN IM nail to those of the IM nails used in developed countries with use of a C-arm.

**Methods:** The terms “Surgical Implant Generation Network” and “union” were searched in four databases. Primary studies of SIGN IM nails were included and their outcomes, including union rate, time to union, and complications, were recorded and compared to historical data of IM nails used in developed countries.

**Results:** Overall, there is a similar union rate in bones fixed with SIGN IM nails (94.6%) versus bones fixed with IM nails in developed countries (92.3%) (p = 0.009, OR = 1.67), while some bone types (tibia and femur) demonstrated a lower union rate when individually stratified (p = 0.008, OR = 0.26 and p = 0.002 and OR = 0.15, respectively). Mean time to union for all bone types combined showed no significant difference between SIGN IM nails and IM nails used in developed countries (p = 0.26). Complications rates were similar between SIGN IM nails and IM nails used in developed countries.

**Conclusion:** It is possible for the SIGN IM nail to be used to fix long bone fractures in developing countries with outcomes comparable to the IM nail used in developed countries.
I. Background ...............................................................................................................................................................

Orthopedic Disease and Injury in Developing Countries ...............................................................................

Standard Treatment for Long Bone Fracture Care: The Intramedullary Nail ..............................................

SIGN Intramedullary Nail ........................................................................................................................................

Cost-Effectiveness of IM nails vs. Skeletal Traction ........................................................................................

Benefits of SIGN IM Nails .........................................................................................................................................

Other SIGN Innovations ........................................................................................................................................

SIGN Database ..........................................................................................................................................................

SIGN Outcomes ........................................................................................................................................................

SIGN IM Nails in Special Situations .......................................................................................................................

SIGN IM Nails in Wartime ........................................................................................................................................

II. SIGN Technique and Design ............................................................................................................................

SIGN as Sustainable Model ................................................................................................................................

Biomechanics The IM Nail is the standard treatment for tibial shaft fractures. In a biomechanical
evaluation, researchers compared the SIGN IM nail for the tibia to the Russel-Taylor tibial nail. A
materials testing machine showed no significant difference between the two nails in terms of
torsional stiffness or total deformity. However, the SIGN nail showed greater stiffness under
axial loading, and greater plastic deformity under cyclical loading than the Russel-Taylor
nail.[136] ....................................................................................................................................................................

Evolution/Different Uses of the SIGN IM Nail ....................................................................................................

Lengthening Over a Nail/Transport Over a Nail ....................................................................................................

III. Future of SIGN .....................................................................................................................................................

IV. Summary ...............................................................................................................................................................

I. Introduction ...........................................................................................................................................................
III. Results

Paper Characteristics

Union Rate

Time to Union

Complications

NR = not reported by authors

2Odds Ratio (95% CI) calculated using Univariate Logistic Regression

Limitations

Conclusion

Synthesis

In developing countries, two billion people do not have access to surgical care. Over 90% of deaths from injury, and 90% of severe fractures happen in developing countries. Many of these injuries require surgical care that may not be available to patients, and in fact injury is the leading cause of death of people in developing countries between 5 and 45 years old. Even though the standard of care for long bone fractures in developed countries is the intramedullary (IM) nail, the cost of IM nails has led to many fractures being treated with the less cost- and clinically-effective skeletal traction in developing countries. Since its inception in 1999, SIGN’s IM nail specially designed for use without a costly image intensifier has been provided at no cost to hundreds of hospitals in dozens of developing countries, transforming fracture care for tens of thousands of patients world-wide.
Comprehensive Review: An Overview of the Surgical Implant Generation Network (SIGN)

Intramedullary Nail

I. Background

Surgery and Global Burden of Disease

In developing countries, two billion people do not have access to surgical care.[1] This lack of access to surgery can be partially attributed to prohibitive cost and deficient resources, such as electricity and radiography.[2],[3],[4]

Orthopedic Disease and Injury in Developing Countries

Five million people die from injuries each year, more than HIV/AIDS, malaria, and TB combined,[5] with more than 90% of these deaths occurring in developing countries.[6] WHO has projected that by 2020, the global disease burden due to injury will increase to 20% (an increase from 12% in 1990).[7] Often, there is a disproportionate amount of musculoskeletal trauma in developing countries.[8] For instance, half of hospital beds in East Africa are occupied with trauma patients,[9] and 90% of severe fractures happen in developing countries.[10] Injury is the leading cause of death in developing countries of individuals between 5 and 45 years old.[11] Additionally, for each person who dies from trauma, 3 to 8 more people are permanently disabled.[12] A major contributor to injury is road traffic accidents,[13] which are the ninth leading cause of disability worldwide.[14] The contribution of road traffic accidents to the injury burden can partially be explained by the trend of motorcycles often becoming family vehicles in developing countries.[15] Other causes of injury include falls, which are related to an increasing elderly population, work-related injuries, and violence.[16]

Cycle of Poverty

Not only do hospitals in developing countries lack resources to surgically treat patients properly, patients in those countries may themselves seek substandard care due to their own
inability to afford treatment.[17] For example, working-age patients go into traction for fractures for months because they can’t afford the implant, translating into poverty for the family for generations.[18] Such a scenario may lead to the loss of a family’s breadwinner or worker, as well as the potential loss of another worker than must serve as caretaker.[19] Long-term injury of a working family member may mean children will work or be sold into labor instead of going to school so the family can survive.[20]

Standard Treatment for Long Bone Fracture Care: The Intramedullary Nail

Often, the best treatment for a long bone diaphyseal fracture is surgical fixation with an intramedullary (IM) nail.[21] Indeed, an international survey comparing treatment preferences found that orthopedic surgeons preferred to use an IM nail for tibia fractures over external fixation, or open reduction, internal fixation.[22]

SIGN Intramedullary Nail

In 1999 Dr. Lewis G. Zirkle, Jr. founded the Surgical Implant Generational Network (SIGN), whose mission is to ‘create equality in fracture care throughout the world.’[23] Dr. Zirkle spent time practicing orthopedic surgery in Vietnam in the 1960s, and for the next thirty years trained surgeons and assisted local health care teams in implementing more effective fracture care treatment.[24] At one point, Dr. Zirkle found that the surgeons he was training in Indonesia couldn’t fix fractures surgically because they didn’t have the materials. Instead they used traction, a technique which often requires prolonged bed rest of 6 weeks or longer,[25] and in some cases a total healing time of several years.[26] Despite superior functional outcomes with the use of IM nails, due to cost and material restrictions skeletal traction is the most common treatment for long bone fractures in the developing world.[27]

Dr. Zirkle describes how the process of forming a new idea begins with conception of the idea, and then tossing around the idea until contributions are made from various relevant fields to conclude with a final product. Through an ‘emerging hunch,’ ideas melded together over time via connected events and thoughts that eventually combined to form one idea: the Surgical Implant Generation Network (SIGN) Intramedullary (IM) Nail.[28] In 1999 Dr. Zirkle, with the
help of Randy Heubner (owner of Acumed)[29] and associates, created the not-for-profit SIGN Corporation.[30]

The SIGN IM nail is implanted, and its distal screws placed via an innovative target arm, which allows for the nail’s use without an image intensifier such as a C-arm.[30a] Additionally, reaming can be done in the SIGN surgeries by hand which allows for the implant’s use without power.[30b] The SIGN IM nail provides materials in a way that can be used with the surgeon’s available resources, and relies on the surgeon’s tactile senses without requiring intraoperative fluoroscopy[31] or power equipment.[32]

The solid, stainless steel design of all SIGN IM nails[32a] is approved by the FDA,[33] and can be used without imaging and power equipment to fix long bone (femur, tibia, and humerus) and hip fractures.[34] The first product of the not-for-profit SIGN Corporation was the SIGN IM nail for the tibia.[35] The SIGN IM nail has continued to expand its application to various procedures, including lengthening and transport over a nail,[36] retrocalcaneal arthrodesis,[37] and infected non-unions.[38] Eventually, SIGN also developed new IM nails for pediatric patients[39] as well as for hip fractures.[40]

Variations of SIGN IM Nails are designed specially to accommodate the diverse anatomy found in different populations.[41] While smaller SIGN fin nails are used in Asian countries, SIGN redesigned and manufactured a new IM nail to accommodate the wider bony canal in African patients.[42] Specific surgical techniques are mentioned in papers advising surgeons how to adapt their skills to varying patient populations.[43] The former chief of orthopaedics in Cambodia described receiving the SIGN IM nail as a breakthrough for his hospital, where there were no traction tables, implants, or working C-arms. Indeed, in 2007 SIGN helped make the transition from standard traction treatment to IM nails for the Emergency Surgical Centre in Battambang, Cambodia that receives all major injuries from its surrounding province.[44]
Cost-Effectiveness of IM nails vs. Skeletal Traction

A lack of resources is responsible for the use of skeletal traction in lieu of IM nails in developing countries. Ironically, the use of less effective treatments for fracture care may not only be a detriment to the patient’s clinical outcome, it may ultimately be more of a financial cost, as well. A cost-effective analysis was used to compare the cost of the SIGN IM nail to Perkins skeletal traction.[45] The 2 groups were compared using hospital per diem costs, operating room time, equipment, use of blood products, physiotherapy, x-rays, and supplies (dressings, drugs, and/or orthotics, pins, frame, cast-brace, SIGN IM nail).[46] The total cost was 121 USD less and the average hospital stay was 17.4 days shorter for patients treated with SIGN IM nail rather than skeletal traction.[47] The authors of the study predicted that the difference between the interventions would have been more pronounced had the surgeons been more experienced with using the SIGN IM nail, leading to even more cost saving benefit in the surgical group.[48] They hypothesized that in an ideal scenario, the cost of treating 1 patient with a SIGN IM nail would be equivalent to the total cost of treating three patients in traction.[49]

Benefits of SIGN IM Nails

In addition to being a more efficient way to treat long bone fractures, the SIGN IM nail potentially offers other advantages. The solid, stainless steel composition of all SIGN IM nails[50] may confer a lower chance of infection due to the decreased area available for biofilm formation.[51] The lack of fluoroscopy use decreases radiation exposure for both the patient and the surgical team.[52] The use of a hand-reamer theoretically decreases the risk of thermal necrosis, and the bone from the flute of the hand-reamer can be used for grafting in the fracture site.[53],[54] The SIGN IM nail also uses slots instead of holes for screw placement, allowing for compression or distraction across the fracture site.[55]
Other SIGN Innovations

SIGN has developed other products and innovations aside from the IM nail. The SIGN distractor distracts telescoped tibia or femoral shaft fragments.[56] SIGN also helped pioneer the use of commonly available hardware equipment in the surgical orthopedic arena, including battery-operated commercial drills, and oscillating drywall saws.[57] SIGN has also developed an inexpensive negative pressure wound therapy system.[58]

SIGN Program

To date, SIGN IM nails are used in 281 hospitals in 52 developing countries, and have healed 139,303 patients.[59] Often, SIGN implants are the only nails available in hospitals in developing countries.[60] 20 SIGN IM nails are distributed free of cost and by request to hospitals in developing countries that become SIGN centers once they start using the product.[61],[62] Surgeons can be trained to use the SIGN IM nail in about one month’s time[63] with provided on-site education,[64] and a close relationship is maintained between the SIGN founder and SIGN surgeons.[65] Each hospital utilizing SIGN technology is required to maintain patient data whose information is forwarded to a central SIGN database to review technique and outcome of the surgeries. The stock of SIGN IM nail is replenished to the SIGN center free of charge once 20 surgeries have been entered into the SIGN database.[66],[67] Doctors who use SIGN IM nails in surgery meet annually at the SIGN conference in Virginia to share knowledge and foster international relationships.[68] SIGN IM nails in developing countries are often used to treat complex fractures[69] that present after a significant delay from injury[70],[71] and require an open reduction.[72]
SIGN Database

The SIGN database contains follow-up information from SIGN surgeries completed in every SIGN center,[73] and is one of the largest trauma databases in developing countries.[74] Pre- and post-operative radiographs, size of implant, fracture pattern, patient demographics, and complications are all documented after each surgery.[75] The SIGN database allows for evaluation of reduction and fixation of the bones, it ensures SIGN nails not being diverted to private hospitals, and also leads to communication about and improvement of the product.[76] SIGN has commented on the relationship between incentive and quality of information - higher quality of information is collected in the database when the resupply of the SIGN IM nail (or strong incentive) is contingent on the information given.[77]

The global burden of injury is significant but poorly documented.[78] The lack of data related to musculoskeletal issues leads to limited funding for research of orthopedic issues in developing countries.[79] Therefore, better data collection on trauma can impact policy in prevention and document the issues that need to be addressed.[80] While the SIGN database can provide insight to burden of trauma in developing countries, its narrow focus on long bone fractures treated with SIGN IM nails, dependence on internet connection, and use of only English, makes it inappropriate for use as a global trauma database (GTD).[81] Therefore, a more comprehensive database is needed for better analysis of the global burden of trauma.[82] Instead, SIGN suggests that the most likely successful approach to developing a GTD is to integrate a database with existing medical record systems.[83] Ideally, a GTD would be available to hospitals at little or no cost, and would use the map local language input in a local system to standard terms in a GTD.[84] The GTD would be an umbrella for different subsets of trauma that could be used to collect information for different organizations and clients who may serve as a source of funding.[85]
**SIGN Outcomes**

Despite the high incentive for surgeons to input data, the rate of post-operative follow-up are low.[86],[87],[88] SIGN postulates that the follow-up cases are probably biased toward difficult or unexpected outcomes.[89] Due to the low-follow up rates, the SIGN database is not suitable for a comprehensive analysis of union rates or complications.[90]

However, since infection is the greatest concern for an orthopedic implant,[91] analyses of the SIGN database was conducted to determine the infection of SIGN IM nail implant surgeries.[92],[93],[94] The results showed a low, acceptable infection rate,[95],[96] comparable to results published in literature from developed countries.[97] Addressing the possible effect low follow up rates could have on reported infection rates, a study of the SIGN database found that follow up above 5% did not result in increased infection rates.[98]

**SIGN IM Nails in Special Situations**

**SIGN IM Nails in Disaster Response**

SIGN IM nails are also distributed free of cost in regions of natural disaster and armed conflict,[99] and the product’s design for use with limited resources makes it particularly useful in such situations.[100] Surgeons trained in SIGN IM nail placement responded to the tsunami in Banda Aceh, Indonesia in 2004, the Great Pakistan Earthquake in 2005, and to the Central Java Earthquake in Indonesia in 2006,[101] and during the Haiti Earthquake in 2011.[102] During these responses, the SIGN teams would work with local surgeons to operate on patients in sparse conditions, sometimes sleeping on the floor during their stay in the region.[103] This led to some of the local surgeons starting to use SIGN IM nails in their own facilities and training surgeons in surrounding areas to also use the SIGN IM nail in their patients.[104] Due to the success of the SIGN teams in these disaster response situations, Dr. Zirkle stresses the importance of working with local surgeons.[105] Dr. Zirkle also suggests that emergency disaster packages of SIGN equipment be kept ready, and trained personnel willing to travel kept on a list to prepare for a disaster response.[106]
Reflecting on the thousands of SIGN IM nail procedures completed in Haiti in 2011, Dr. Zirkle affirms the crucial role of the local surgeons in saying that the healthcare team should be the primary caregivers with foreign surgeons as accessories in disaster response.[107] Dr. Zirkle emphasizes the importance in maintaining principle surgical standards for sterilization and treatment during disaster response.[108] When the SIGN team left Haiti, they left SIGN nails to the local surgeons once they felt they were adequately trained and had a sterile environment.

SIGN IM Nails in Wartime

The trauma encountered and treated in wartime can catalyze advances in surgery.[109] Extremity injuries are particularly common for orthopedic surgeons to encounter during war.[110] The typical IM nail cost and dependence on fluoroscopy often prohibits its use in war in developing countries.[111] SIGN IM nails were first used in Iraq at US military hospital to treat Iraqi civilians in 2005, and one year later began their use in Iraqi civilian hospitals.[112] After SIGN IM nail’s introduction to Afghani hospitals in 2007, SIGN IM nails have now been for use in the four hospitals in the Afghan National Army health system.[113]

II. SIGN Technique and Design

The SIGN IM nail is used worldwide by a diverse array of orthopedic surgeons.[114] A manual was made by SIGN to explain the procedure for surgical implantation of the SIGN IM nail.[115] Yearly SIGN conferences,[116],[117],[118],[119] online forums,[120] and mutually beneficial partnerships with various departments and institutions[121],[122] allows for shared knowledge and collaboration to advance SIGN product development and innovation.[123] Such collaborations bring insight and new knowledge to SIGN, leading to frequent revisions and updates to the SIGN technique manual.[124] Such insight includes discovery of anatomical nuances in different patient populations, and insight into a particular surgical technique that leads to evolution of the SIGN program.
SIGN as Sustainable Model

Historically, medical surgical missions to developing countries may typically leave patients with poor follow-up care and don’t connect to local healthcare infrastructure for support collaboration.[125] This type of global healthcare intervention can lead to dependency rather than sustainable change.[126] An alternative involves teaching and training the local healthcare staff in implementing the intervention.[127] This is exactly how SIGN operates – training local surgeons in developing countries to use the SIGN IM nail in their own countries, with some hospitals having become SIGN training centers themselves.[128]

Patient Populations

SIGN produces modified designs and surgical technique recommendations according to the anatomical characteristics of specific patient populations in different countries. One study focused on the optimal entry point of a SIGN IM tibial nail for retrograde femoral nailing in Thai patients.[129] Also, while smaller SIGN fin nails are used in Asian countries, SIGN redesigned and manufactured a new IM nail to accommodate the wider bony canal in African patients.[130] Specific surgical techniques are mentioned in papers advising surgeons how to adapt their skills to varying patient populations.[131]

Technique

Distal interlocking screw placement is the hardest part of IM nail placement, and some surgeons noted that the SIGN IM nail was no exception.[132] A patient’s SIGN IM nail migrated to the knee one year postop because the distal screw missed the slots. Therefore, the surgeons worked to determine supplemental instructions to help minimize error in distal screw placement of the SIGN IM nail, which are especially important for surgeons new to the SIGN technique.[133] Some studies advise on the appropriate time frame in which to perform closed versus open fracture reductions,[134] other papers suggest positions for patients during operations, and reaffirm to SIGN surgeons that their tactile senses are reliable in placing the SIGN IM nail without fluoroscopy.[135]
**Biomechanics**

The IM Nail is the standard treatment for tibial shaft fractures. In a biomechanical evaluation, researchers compared the SIGN IM nail for the tibia to the Russel-Taylor tibial nail. A materials testing machine showed no significant difference between the two nails in terms of torsional stiffness or total deformity. However, the SIGN nail showed greater stiffness under axial loading, and greater plastic deformity under cyclical loading than the Russel-Taylor nail.[136]

One paper describes the creation of the SIGN IM nail for hip fractures, in which load-to-failure testing, then fatigue testing on composite femurs was used to shape the implant’s design.[137] As clinical time is limited, the value of ex-vivo testing of the implants was noted by the author.[138] Both a fin IM nail and an IM nail with distal interlocking screws were designed based on the results of the biomechanical testing.[139] The fin nail doesn’t use distal screws; instead its distal end is designed to interdigitate with the bone canal via compression fit, a design suitable for bones in countries such as Cambodia and Myanmar.[140] In countries whose patients have larger bone canals, such as Africa, the IM nail with the distal interlocking screw was created for fixing hip fractures.[141] The researchers in this investigation commented that there is no consistent or ‘universally accepted test standard for biomechanical testing of hip fractures constructs,’ making it impossible to compare the results of the SIGN IM nail for the hip to other studies testing the same type of constructs.[142] The author suggests that dynamic loading best simulates physiological loading, and is therefore a superior candidate for a standardized method of testing hip implants.[143]

**Evolution/Different Uses of the SIGN IM Nail**

The SIGN IM nail was originally developed in 1999[144] for use in tibia fracture fixation.[145] Now, the same SIGN IM nail originally intended for the tibia has been adapted for use in fixing of the femur and humerus.[146] The SIGN IM nail has continued to expand its application to various procedures, including lengthening and transport over a nail[147], retrocalcaneal arthrodesis[148], and infected non-unions.[149] Eventually, SIGN also developed new IM nails for pediatric patients[150] as well as for hip fractures.[151]
**Lengthening Over a Nail/Transport Over a Nail**

Surgeons performing lengthening over a nail (LON) and transport over a nail (TON) procedures stated that they preferred to use the SIGN IM nail for its lower cost, solid cross-section, excellent fatigue strength, and 8 mm nail availability in various tibial nail lengths.[152] They said that the SIGN IM nail worked well and that more expensive implants are not required.[153]

**Retrocalcaneal Arthrodesis**

Another group used the SIGN IM nail retrocalcaneal athrodesis for non-reconstructable distal tibia or talus fracture, suggesting the plantarmedial calcaneus in line with tibial shaft as the starting point.[154]

**Femur fracture fixation**

The first SIGN surgery in a femur was implanted with a retrograde approach using a tibial SIGN IM nail in 2000 in Vietnam.[155] Full flexion was achieved postoperatively, and surgeons in South East Asia subsequently adopted the approach.[156]

**Hip fracture fixation**

Dr. Zirkle wrote a paper to describe the SIGN Hip Construct, a 300 mm SIGN IM fin nail or nail with distal slots implanted through a trochanteric entry point, that had its first clinical use in Afghanistan.[157] The authors commented that in developing countries, there is often a delay between injury and presentation, and hip fractures in Afghanistan were usually treated with 3 weeks of traction then discharged in body cast.[158] The sliding hip screw may have been a surgical option in some cases, however it requires the use of a C-arm.[159] Therefore, the SIGN Hip Construct offers an alternative to traction for hip fractures that can be done without the use of a C-arm.[160] In describing the SIGN Hip Construct technique, Dr. Zirkle emphasizes the important role of distal fixation to the overall stability of the construct.[161] He states that some subtrochanteric fractures may be fixed with a standard SIGN nail.[162] The SIGN Hip Construct can be implanted using a regular operating table (a fracture table is not necessary) in the lateral position.[163] Dr. Zirkle emphasizes the importance of instructing the patient’s
family on postoperative weight-bearing as tolerated by the patient, as some cultures may think that rest is preferred after a surgery.[168] Dr. Zirkle advises that surgeons try to preserve callus in intertrochanteric fractures.[169] Currently, the SIGN Hip Construct is used in multiple SIGN programs in Africa, including Tanzania, Uganda, and Kenya.[170]

III. Future of SIGN

Disruptive Innovation

The SIGN IM nail is a disruptive innovation[171] that originally was designed for use in developing countries, but can be used to impact the healthcare landscape of developed countries, as well.[172],[173] The concept of disruptive innovations is used to describe “cheaper, simpler, more convenient products or services that start by meeting the needs of less-demanding customers.”[174] Products initially designed as technologically inferior but cheaper products to target low end of market eventually improve as a product to be able to target most of the market.[175] The performance trajectory allows products, such as the SIGN IM nail to eventually meet demands of more sophisticated consumers.[176] On the opposite end of the spectrum from disruptive innovations are sustaining innovations - products targeting the higher end of market invested in continuing to become more progressive.[177] Sustaining products don’t address limited access of product to the lower end of market, and disruptive innovations capitalize on this gap by introducing a product below sustaining innovations to the lower end of the market.[178] In medicine, sustaining innovations manifest as specialists, emerging technologies, and focusing on the sickest patients.[179] In orthopedics, organizational structures and incentives often result in a disproportionate focus on sustaining innovations.[180] Christensen suggests that the “phenomenon of overshooting the needs of the average consumer and creating the potential for disruption quite accurately describes the current situation faced by the healthcare industry.”[181] One disruptive innovation in orthopedics is the mini C-arm, which, while not offering the same image quality or functionality as a regular c-arm, offers a simple and mobile imaging option that can be used for lower complexity cases at a lower cost and with less radiation exposure.[182] Likewise, the highly versatile, easy-to-use SIGN IM nail offers a low-tech and low-cost option for IM nail implants in
developing countries without requiring power drills or fluoroscopy.[183] Similar disruptive innovations can also be seen in the rest of medicine with the addition of physician assistants and nurse practitioners, and ambulatory surgical centers that help to increased access to quality healthcare at lower cost.[184] Theoretically, disruptive innovations offer lower cost, more efficient, and more convenient alternatives to sustaining innovations and may improve quality of care.[185] Despite the potential benefits, the healthcare environment’s resistance to change, actions by regulatory bodies, and support for status quo to maintain position and profit can hinder disruptive innovations from being streamlined into market use.[186] While insurance companies should intuitively be allies of cost-effective products to keep check on profit margins, they will only reimburse for procedures that are peer-reviewed and comparable to the ‘gold standard,’ which often stifles new products.[187] Lack of published research demonstrating product efficacy, lengthy FDA approval processes, and intellectual property laws also contribute to the stifling of disruptive innovations.[188] To improve national health, resources need to be directed toward improving access and affordability, and addressing needs of the majority.[189] Not actively pursuing disruptive innovations will lead to worsening of the healthcare financial burden.[190]

SIGN as Sustainable Investment

The SIGN IM nail is a disruptive innovation that has increased access worldwide to quality healthcare at a lower cost.[191] SIGN is a not-for-profit corporation currently supported by private donations, service clubs, and industries.[192] SIGN IM nails are given free of charge to participating programs, however growing or maintaining the programs supply of implants is challenging.[193] While one study demonstrated the cost benefit of the SIGN procedure over traction[194] further cost effectiveness analyses alongside clinical trials would be “useful in advocating for investment in an intervention and allow comparison across many different prevention and treatment strategies.”[195]

The SIGN IM nail costs much less than Western IM nails,[196] is associated with a low infection rate, and is an easy to master procedure[197] that bypasses requirements for power or fluoroscopy.[198] The characteristics of the SIGN IM nail make it ideal for resource-poor
countries,[199] and the product is applicable for routine use in North America, as well.[200] Beyond the IM nail, SIGN continues to research topics such as non-unions, bone loss, drill covers, femoral neck fractures, patient education, and the potential use of fracture braces for closed tibial fractures in place of SIGN IM nails.[201]

The U.S. has a percent health expenditure of 16%, with a projected to increase to 30% in 2035.[202] Musculoskeletal issues are the leading cause of disability, accounting for more than half of all chronic conditions in people over 50 years old.[203] Tens of millions of people are affected by spine conditions, arthritis, joint pain, and the cost of musculoskeletal-related disorders in 2004 was $849 billion, equaling 7.7% of the GDP.[204] The far reaching-effects[205] of the SIGN IM nail makes SIGN a sustainable investment[206] for all countries. Investment can be done in the context of social entrepreneurship.[207]

IV. Summary

Lack of access to surgery, which can be partially attributed to prohibitive cost and deficient resources, is a major cause of morbidity and mortality in developing countries.[208-212] 90% of severe fractures occur in developing countries,[213] and due to cost these are often treated with a prolonged and sub-optimal treatment of skeletal traction instead of the more ideal IM nailing.[214] The SIGN IM nail, provided to developing countries free of charge, increases access of IM nailing to patients in need. When considering global health initiatives, it is important from an ethical perspective to maintain the quality of an intervention to clinical standards to avoid providing sub-optimal care to a population just because the intervention is affordable. Analyzing the clinical outcomes of fractures fixed with SIGN IM nails to determine if they are comparable to IM nails used in developed countries is important to upholding standards of equitable medical care.

Due to the low-follow up rates, the SIGN database is not suitable for a comprehensive analysis of union rates or complications.[215] There are retrospective and prospective studies of SIGN IM nails in the literature that report the outcomes of fractures fixed with SIGN IM nails. The purpose of this systematic review and meta-analysis is to gather outcome data from such
papers and determine if SIGN IM nails have a comparable clinical outcome, in terms of rate of union, time to union, and infection rate, as IM nails used in developed countries.
I. Introduction

In developing countries, two billion people do not have access to surgical care.1 This lack of access to surgery can be partially attributed to prohibitive cost and deficient resources, such as electricity and radiography.2,3,4 Over 90% of deaths from injury,5 and 90% of severe fractures happen in developing countries.6 For each person who dies from trauma, three to eight more people are permanently disabled.7

The standard of care for long bone fracture fixation surgery is a closed intramedullary (IM) nail surgery with the use of an intraoperative image intensifier;8 an international survey found that orthopedic surgeons preferred the IM nail for tibia fractures over external fixation, or the plate.9 Despite superior functional outcomes with the use of IM nails, skeletal traction is the most common treatment for long bone fractures in the developing world.10 According to the World Health Organization (WHO), working-age patients go into traction for fractures for months because they can’t afford the implant, translating into poverty for the family for generations.11 In 1999 Dr. Lewis G. Zirkle, Jr. founded the Surgical Implant Generational Network (SIGN), whose mission is to ‘create equality in fracture care throughout the world.’12 In Dr. Zirkle’s experience, the use of traction instead of IM nails is usually due to lack of resources.13

The solid, stainless steel14 design of all SIGN IM nails15 is approved by the FDA,16 and can be used without an image intensifier (such as a C-arm) or power equipment to fix long bone (femur, tibia, and humerus) and hip fractures.17,18 20 SIGN IM nails are distributed free of cost and by request to hospitals in developing countries that become SIGN centers once they start using the product.19,20 Surgeons can be trained to use the SIGN IM nail in about one month’s time21 with provided on-site education,22 and a close relationship is maintained between the SIGN founder and SIGN surgeons.23 The stock of SIGN IM nail is replenished to the SIGN center free of charge once 20 surgeries have been entered into the SIGN database.24,25 A cost-effective analysis revealed a decreased total cost and decreased average hospital stay for patients whose
fractures were fixed with the SIGN IM nail as compared to skeletal traction.26,27 To date, SIGN IM nails are used in 281 hospitals in 52 developing countries, and have healed 139,303 patients.28

Determining the clinical outcomes of fractures fixed with SIGN IM nails to see if they are comparable to IM nails used in developed countries is important to the process of maintaining standards of equitable medical care for populations who benefit from this global health initiative. Due to low-follow up rates, the SIGN database is not suitable for a comprehensive analysis of union rates or complications.29 There are some retrospective and prospective studies of SIGN IM nails in the literature that analyze the outcomes of fractures fixed with SIGN IM nails. The purpose of this systematic review and meta-analysis is to determine if SIGN IM nails have a comparable clinical outcome, in terms of rate of union, time to union, and infection rate, as IM nails used in developed countries.

II. Methods

The terms “Surgical Implant Generation Network” and “outcome” were searched in the PubMed, Embase, Cochrane, and Techniques in Orthopaedics databases. The results of the search are outlined in Figure 1. Included in this review and meta-analysis were primary studies published from 1999 to 2015 that provided empirical data regarding clinical outcome, including bony union, of bones fixed with SIGN intramedullary nails. Excluded were articles that were not written in the English language and were not found in one of the four databases mentioned above. 26 articles identified through the initial database searches were screened and those whose titles did not meet inclusion criteria, as well as duplicates, were removed. The abstracts of the remaining 14 articles were screened and 1 that did not meet the inclusion criteria was removed. The full texts of the remaining 13 articles were read and 1 article that did not meet the inclusion criteria was removed. The references of the remaining 12 articles were reviewed for relevant articles, yielding 21 additional articles after duplicates were removed. Based on full reading of the texts, all 21 of the additional articles were removed due to not meeting the inclusion criteria or meeting the exclusion criteria. The final set of 12 included articles of SIGN IM nails were read and their outcomes, including union rate, time to union, and complications,
were recorded and compared to the IM nail used in developed countries using historical data. Chi squared analysis and univariate logistic regression that reports OR at 95% confidence intervals were used to compare union rates between fractures fixed with SIGN IM nails and IM nails used in developed countries. The one sample t-test was used to compare time to union of fractures fixed with SIGN IM nails versus IM nails used in developed countries. The number of complications reported for SIGN IM nails were compared to the number of complications reported for IM nails used in developed countries.
Fig. 1 Flow chart of systematic literature search in PubMed, Embase, and Cochrane Library Databases and from other sources based on PRISMA Guidelines
III. Results

12 articles met the inclusion criteria and were gathered from a search of the PubMed, Embase, Cochrane, and Techniques in Orthopaedics databases. These 12 articles were primary studies that reported union rate outcomes on fractures of femurs, tibias, and humeri fixed with SIGN IM nails. The surgical procedures covered in these studies included long bone fracture fixation, infected non-union, ankle arthrodesis, and lengthening over a nail.

Paper Characteristics

A summary of the studies including number of limbs in each study, the percentage of fractures fixed with the SIGN IM nail that united, the mean time to union of those fractures, and the mean duration of injury prior to surgery are listed in Figure 2.

Union Rate

Taking all bone types into consideration, there is a similar union rate in bones fixed with SIGN IM nails (94.6%) versus bones fixed with IM nails in developed countries (92.3%) (p = 0.009, OR = 1.67). Some bones (tibia and femur) demonstrated a lower union rate when those bone types were individually stratified (p = 0.008, OR = 0.26 and p = 0.002 and OR = 0.15, respectively). The union rate of all bone types combined and stratified by bone type with P values and OR is listed in Figure 3.

Time to Union

Time to union for all bone types combined showed no significant difference in mean time to union between SIGN IM nails and the established treatment (p = 0.26). Time to union of fractures fixed with SIGN IM nails compared to the standard IM nails used in developed countries for both all bones combined and stratified by bone type per study is listed in Figure 4.

Complications

Complication rates reported in fractures fixed with SIGN IM nails were similar to those reported in fractures fixed with IM nails used in developed countries. Figure 5 displays the reports of complications of fractures fixed with SIGN IM nails by paper.
<table>
<thead>
<tr>
<th>Study (author)</th>
<th>Area of fixation</th>
<th># limbs</th>
<th>% united</th>
<th>Mean time to union (weeks)</th>
<th>mean duration of injury prior to surgery (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikem et al.</td>
<td>femoral shaft, tibial shaft, humeral shaft</td>
<td>34</td>
<td>100%</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>34</td>
<td>100%</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Lwin et al.</td>
<td>tibio-talar calcaneal fusion</td>
<td>16</td>
<td>93%</td>
<td>16</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>15</td>
<td>93%</td>
<td>16</td>
<td>NR</td>
</tr>
<tr>
<td>Shah et al.</td>
<td>tibia</td>
<td>36</td>
<td>100%</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Khan et al.</td>
<td>tibia</td>
<td>50</td>
<td>92%</td>
<td>23.3</td>
<td>14</td>
</tr>
<tr>
<td>Stephens, et al.</td>
<td>tibia</td>
<td>162</td>
<td>97.3%</td>
<td>15</td>
<td>4.1</td>
</tr>
<tr>
<td>Zain-ur-Rehman et al.</td>
<td>tibia</td>
<td>80</td>
<td>80%</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>80.5</td>
<td>92.3%</td>
<td>18.1</td>
<td>7.5</td>
</tr>
<tr>
<td>Shah et al.</td>
<td>Tibia and femur</td>
<td>250</td>
<td>100%</td>
<td>16</td>
<td>NR</td>
</tr>
<tr>
<td>Soren et al.</td>
<td>Tibia and femur</td>
<td>80</td>
<td>93%</td>
<td>18.5</td>
<td>NR</td>
</tr>
<tr>
<td>Ikpeme et al.</td>
<td>Tibia and femur</td>
<td>37</td>
<td>97.3%</td>
<td>16.9</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>113.3</td>
<td>96.67%</td>
<td>17.1</td>
<td>NR</td>
</tr>
<tr>
<td>Naeem-Ur-Razaq et al.</td>
<td>Femoral shaft</td>
<td>47</td>
<td>97.83%</td>
<td>19.7</td>
<td>1-7 (avg 3)</td>
</tr>
<tr>
<td>Pantti et al.</td>
<td>Femoral shaft</td>
<td>48</td>
<td>84.4%</td>
<td>NR</td>
<td>12.2</td>
</tr>
<tr>
<td>Sekimpi et al</td>
<td>Femoral shaft</td>
<td>50</td>
<td>100%</td>
<td>NR</td>
<td>13.2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>48.3</td>
<td>91.67%</td>
<td>19.7</td>
<td>9.5</td>
</tr>
<tr>
<td>Total (Mean, All Bones)</td>
<td></td>
<td></td>
<td>94.6%</td>
<td>17.1</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Figure 2. Table summarizing studies by area of fixation including number of limbs in each study, the percentage of fractures fixed with the SIGN IM nail that united, and the mean time to union of those fractures

NR = not reported by authors
<table>
<thead>
<tr>
<th>Bone Type</th>
<th>Standard Treatment (n)</th>
<th>SIGN (n)</th>
<th>P-Value&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Odds Ratio (95% CI)&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All combined</td>
<td>1169</td>
<td>773</td>
<td>0.009</td>
<td>1.67 (1.12, 2.52)</td>
</tr>
<tr>
<td>Femur Only</td>
<td>438</td>
<td>137</td>
<td>0.002</td>
<td>0.15 (0.03, 0.59)</td>
</tr>
<tr>
<td>Tibia Only</td>
<td>157</td>
<td>245</td>
<td>0.008</td>
<td>0.26 (0.06, 0.78)</td>
</tr>
<tr>
<td>TTC</td>
<td>556</td>
<td>14</td>
<td>0.7</td>
<td>2.14 (0.31, 91.5)</td>
</tr>
<tr>
<td>Femur + Tibia + Humerus</td>
<td>613</td>
<td>40</td>
<td>1.0</td>
<td>0.71 (0.10, 31.6)</td>
</tr>
<tr>
<td>Tibia + Femur</td>
<td>595</td>
<td>337</td>
<td>1.0</td>
<td>0.90 (0.25, 3.6)</td>
</tr>
</tbody>
</table>

*Figure 3. Union Rate of all bone types combined and stratified by bone type*

<sup>1</sup>*P-value calculated using Chi-Squared analysis*

<sup>2</sup>*Odds Ratio (95% CI) calculated using Univariate Logistic Regression*
Figure 4. Time to union of SIGN IM nails vs. standard IM nails used in developed countries for both all bones combined and stratified by bone type per study.
Figure 5. Complications of Fractures Fixed with SIGN IM nails.
IV. Discussion

Majority of the world’s morbidity and mortality related to injury occurs in developing countries, where prohibitive costs and deficient resources play a part in these populations’ limited access to surgical care.\textsuperscript{30,31,32,33,34,35} While the standard of care for long bone fractures in developed countries is IM nail fixation guided by an image intensifier such as a C-arm,\textsuperscript{36} such equipment is scarce in developing countries. This has led to fracture care in developing countries consisting mainly of traction, which leads to poorer clinical outcomes\textsuperscript{37} and is less cost-effective than IM nails.\textsuperscript{38} Since its inception in 1999, SIGN’s IM nail specially designed for use without an image intensifier has been provided at no cost to hundreds of hospitals in dozens of developing countries, transforming fracture care for tens of thousands of patients world-wide.\textsuperscript{39,40,41} While SIGN maintains a database recording all the uses and outcomes for each SIGN nail used in each country,\textsuperscript{42} no review has been completed on the more focused observational cohort studies of patients treated with SIGN nails in individual hospital settings.

This analysis demonstrates that the outcomes for the fractures fixed with SIGN IM nails in these studies, including union rate and complications, were similar to outcomes of IM nails typically used in developed countries. SIGN IM nails, therefore, provide an affordable fracture fixation option for patients in developing countries with outcomes comparable to the standard of care for fractures in developed countries.

Limitations

There were some limitations to this systematic review and meta-analysis. Papers either did not report, or reported a relatively long average duration of injury prior to surgery (range: 1 to 13 days). The outcomes were compared to fractures fixed with IM nails in developed countries, where there is typically a shorter duration of injury prior to surgery. A delayed time to treatment could impact the outcomes of the surgical fixation of the fractures, and the varying durations of injury prior to surgery may be reflected in the clinical outcomes.

Papers either had varying definition for radiographic union and clinical union criteria, or did not report their definition for union. A lack of consistent definitions for fracture union hinders the ability to accurately analyze the results for this outcome in a standardized fashion. In future studies of clinical outcomes of SIGN IM nails, standardized criteria for union could be
useful in creating a consistent way of assessing the efficacy of SIGN IM nails. One option could be using the “squat and smile” method whereby patients who are able to smile while squatting after their SIGN surgery signifies a clinically successful procedure.

The SIGN nail is a project that has revolutionized fracture care for tens of thousands of patients in developing countries worldwide. In many ways, the SIGN nail can be viewed as a “disruptive innovation,” a concept introduced by Clayton Christensen of the Harvard Business School to describe “cheaper, simpler, more convenient products or services that start by meeting the needs of less-demanding customers.” These is in contrast to “sustaining innovations” that target the higher end of the market and continually invest in getting more progressive. Christensen suggests that some medical specialties disproportionately focused on expensive sustaining innovations rather than disruptive innovations because of organizational structures and incentives. Another example of a disruptive innovation is using a relatively inexpensive ultrasound as an initial imaging tool, rather than a costly CT scan. While an ultrasound may technically have a lower quality resolution than a CT scan, the practicality and cost-effective benefit outweighs the sacrifice of higher quality imaging and is an acceptable diagnostic tool that has transformed medical care. This review and meta-analysis demonstrates that the SIGN nail is a technological innovation that offers an affordable alternative for fracture care without sacrificing quality or outcome.

**Conclusion**

It is possible for the SIGN IM nail to be used to fix long bone fractures in developing countries with outcomes comparable to the IM nail used in developed countries.
Synthesis

In developing countries, two billion people do not have access to surgical care.\textsuperscript{44} Over 90\% of deaths from injury,\textsuperscript{45} and 90\% of severe fractures happen in developing countries.\textsuperscript{46} Many of these injuries require surgical care that may not be available to patients, and in fact injury is the leading cause of death of people in developing countries between 5 and 45 years old.\textsuperscript{47} Even though the standard of care for long bone fractures in developed countries is the intramedullary (IM) nail, the cost of IM nails has led to many fractures being treated with the less cost- and clinically-effective skeletal traction in developing countries.\textsuperscript{48,49} Since its inception in 1999, SIGN’s IM nail specially designed for use without a costly image intensifier has been provided at no cost to hundreds of hospitals in dozens of developing countries, transforming fracture care for tens of thousands of patients world-wide.\textsuperscript{50,51,52}

Since 1999, the SIGN IM nail’s stainless steel model has evolved to fix the femur, tibia, humerus, and hip.\textsuperscript{53,54} In light of SIGN’s expanding reach, determining the clinical outcomes of fractures fixed with SIGN IM nails to see if they are comparable to IM nails used in developed countries is important in upholding standards of equitable medical care for more vulnerable populations. While SIGN has a database where data from all surgeries involving SIGN IM nails are input by SIGN surgeons world-wide,\textsuperscript{55} the SIGN database is not suitable for a comprehensive analysis of union rates or time to union due to the low-follow up rates.\textsuperscript{56} Therefore, this paper created a systematic review and meta-analysis of focused, retrospective and prospective studies of fractures fixed with SIGN IM nails in developing countries to assess if the clinical outcomes were comparable to fractures fixed with IM nails used in developed countries.

The outcomes for the fractures fixed with SIGN IM nails in these studies, including union rate, time to union, and complications, were similar to outcomes of IM nails typically used in developed countries. SIGN IM nails, therefore, provide an affordable fracture fixation option for patients in developing countries with outcomes comparable to the standard of care for fractures in developed countries. Although there were some limitations in that the included studies were not randomized controlled trials, and were assessing fractures fixed with SIGN IM nails after a relatively delayed time from injury to presentation and surgery, it can be concluded
that it is possible for the SIGN IM nail to be used to fix long bone fractures in developing countries with outcomes comparable to the IM nail used in developed countries. Another limitation was the variability in the way that papers defined fracture union – authors had different radiographic and clinical markers of union, or a combination of the two, that led to an inconsistency in how the data was combined to reach mean values for time to union and union rate.

Overall, it is reassuring that the time to union, union rate, and complication rate were comparable between SIGN IM nails and IM nails used in developed countries, indicating that SIGN indeed provides equitable, accessible fracture care to populations in need. Future studies could be conducted with a standard definition of union to better compare results between studies. Perhaps such a definition could be tailored to a low-resource setting to decrease the need for extensive or costly follow up such as radiographic imaging. One such solution could be a “squat and smile” test wherein patients could even do a video call with the surgeon (often patients live far from hospitals and travel is impractical) to show that they can smile while squatting, signifying bony union of the limb fixed with a SIGN IM nail. Since the results show that SIGN IM nails have comparable clinical outcomes to IM nails used in developed countries, perhaps future studies could include randomized controlled trials in developed countries between SIGN IM nails and commercial IM nails in patients with similar demographics in order to control for nutritional status, time from injury to surgery, and injury severity.

First created for “less demanding customers”\textsuperscript{57} (i.e. patients in developing countries), the SIGN IM nail is a “disruptive innovation” that could also potentially lower fracture care costs for patients in the developed world. SIGN is an example of people in the developed world creating innovative, low cost, but adequate products driven by low-resource settings, that in turn can benefit and lower healthcare costs for people in the developed world. In this way, SIGN represents an ideal symbiotic relationship between the developed world and the developing world that can hopefully inspire a paradigm and perspective for the future of Global Health.


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[8] Ibid.


[12] Ibid.


[20] Ibid.


[43] Ibid.


[45] Ibid.

[46] Ibid.

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[61] Ibid.


[63] Ibid.


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