Radiation-free Micron-resolution Monitoring of Orthopedic Implant Stability

1. Elevator Pitch

Introduction: OrthoDx is developing a system to precisely monitor the dynamic stability of an orthopaedic implant by measuring its movements with respect to the host bone under varying loads representative of ordinary daily activity. Short, non-intrusive and radiation free regular monitoring sessions collect data indicative of the healing process. After healing, periodic monitoring provides early warning of implant loosening to facilitate efficient intervention and improved prognosis.

The Customer: Although hospitals will be the end buyers of our technology, health insurers, the "payors", will reimburse the hospitals for the device. Prosthesis designers and manufacturers currently rely upon expensive radiostereometric analysis (RSA) for prosthesis assessment. OrthoDx can replace RSA with a system that provides more precise data than RSA at a great cost savings and with more convenience. Therefore, manufacturers are potential customers. This is confirmed by the discussions we have had with major players. J&J, Stryker, Nuvasive, etc.

The Need: Component loosening, be it septic or aseptic, is a major cause of joint replacement failure. During the early post-operative period following joint replacement surgery, studies suggest motions between the implant and the host bone should not exceed 150 microns to promote solid osseointegration and lessen the possibility of fibrous union formation.[1] Fast and precise monitoring means remedial measures designed to preserve the integrity of the construct may be instituted in a timely manner, thereby lessening the payor burden of costly revision surgery. For the orthopedist, having a clear picture of movement in the hip would be a game changer, allowing doctors to prescribe a personalized series of steps for patients from simple modification of weight bearing, to pharmacologic intervention[2] or revision surgery when necessary. Currently despite the availability of multiple diagnostic tools, the ability to accurately diagnose an early-stage loose prosthesis hovers at less than eighty percent.[3]

Our first target population is the 500,000 or so patients receiving hip replacements every year. It is conservatively estimated that 10% of patients will have post-operative symptoms requiring further evaluation to rule out possible loosening or infection (costing at least $1,699 for imaging). Further, of all total joint replacements done each year, primarily hip and knee, approximately 10% are revision surgeries costing on average $77,851 per surgery.[4]

Our technology is widely applicable. After implementing our device within hip replacement, we intend to expand our solution to all procedures that require the stability of the construct to be monitored, i.e., all joint replacements, spine fusions, fracture care, arthrodesis, joint reconstruction, etc.

The Value Proposition: The potential value of our technology is apparent within five main audiences:

- Payors: Reduce costs of repeat surgeries ($77,851 per surgery) through prompt intervention; Lessen costs of diagnostic imaging (at least $1,699 per patient)
- Providers/Orthopedists: Early warning of potential loosening issues (particularly pertinent with infection concerns); Decrease revision surgeries through early diagnosis of pathological motion; Increase osseointegration through individualized treatment
- Patients: Lessen the need for revision surgery through early detection of pathologic motion; Peace of mind; Decreased exposure to radiation; Decreased time and costs of post-surgical procedures; monitoring procedure simple enough that patients can potentially do it themselves, enabling virtual doctor/patient interactions
- Manufacturers: Lower cost, higher precision research and clinical implant data
- Pharmaceutical Companies: Precise measurement of response to osteogenic promoting drugs

The Innovation: The proposed innovation is an implanted wireless microsensor technology that provides critical real time detection of implant loosening at micron scale. It uses miniaturized, low-cost, electromagnetic sensors (MMS) placed within the host bone during surgery. These are subsequently addressed by a specialized antenna and computing equipment external to the patient. No x-rays are needed. When addressed, each sensor generates an electromagnetic field that measures the proximity of the implant and transmits this measurement data to the Wireless Communication Module (WCM). A standard desktop computer connected to the WCM, (not shown in Figure 1), processes these data and displays the results.

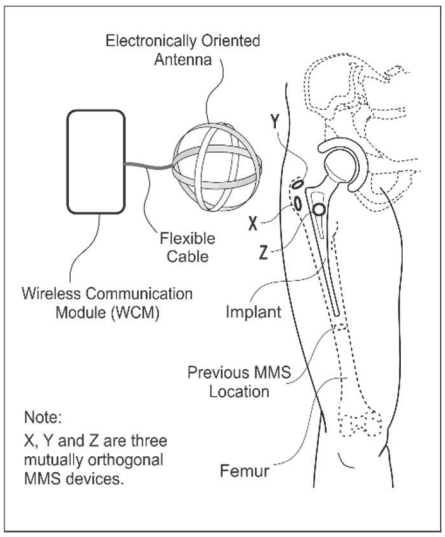


Figure 1. Conceptual drawing of the OrthoDx Implant Stability Monitoring System showing how its components are arranged to monitor loosening.

Figure 1 to the right has been updated to reflect the goals of this proposal. The item labelled "Previous MMS Location" represents our initial single axis prototype sensor concept. This earlier iteration MMS was located distally within the femoral intramedullary canal where it could sense vertical motion of the implant relative to the host bone. We now propose to replace this concept with a superior three-axis sensing scheme consisting of the cluster of mutually orthogonal sensors labelled X, Y, Z. These would be placed within the greater trochanter region as illustrated in Figure 1. We have decided on three-axis sensing for several reasons:

- Although a loosened implant will eventually exhibit vertical motion parallel to the long axis of the femur, other motions may occur first. Gradual osteolysis may erode fixation in a way that causes the implant to initially twist or pivot or tilt sideways. Three-axis sensing will detect such motions, which may be important early indicators of loosening that would be missed if sensing only vertical motion.
- The three sensors can be placed during initial surgery or percutaneously at any time thereafter, which means ***our sensing system can be offered to patients who already have an implant.***
- The three sensors can be of smaller diameter because they can be placed after the implant has been seated. The placement procedure can thus be more precise, and the sensors can be positioned closer to the surface of the implant for greater measurement resolution.
- If clinically necessary, the three ***sensors can be easily retrieved or repositioned***. (A major drawback of the intermedullary sensor is that it could not be easily retrieved.)

When placing sensors during surgery, it is not necessary to align the X, Y, Z sensors to any frame of reference. Three mutually orthogonal sensors provide complete orientation data that can be translated to any reference frame. This makes it easier to find suitable locations for these sensors. The sensors need not be in a precisely orthogonal relationship but should be within +/- 10 degrees of orthogonal. (A more detailed explanation of how the system works is in section 15 below.)

Please note: This document proposes a three-axis system but relies upon our successful research and functional prototype of a single-axis system having a single 10 mm diameter sensor placed within the femoral canal. To prepare for this next step we have physically verified what is theoretically obvious, which is that the sensor can be scaled down and can be located within the greater trochanter, and that the same physics and method of sensing works just as well in this proximal location as it did in the distal location. We now propose to build such a three-axis system to serve as a prototype suitable for demonstration and to

facilitate further validation such as cadaver testing. (A more detailed presentation of our goals is found in section 18 below.)

To truly monitor and improve joint replacement success, a sensor must measure movement in microns throughout the life of the joint. Our simple and durable sensor requires no battery and stays dormant until externally powered and addressed. ***MMS sensor lifetime is expected to equal or exceed that of the implant it monitors.*** Measurements may be taken conveniently in an office setting during gait analysis, or even at home by the patient. (We envision making the system very easy to use.)

2. The Commercial Opportunity

There is a growing societal need for hip replacement surgery. Osteoarthritis (OA) of the hip is among the most prevalent and disabling conditions affecting middle-aged and older adults, causing pain, gait abnormalities and functional impairments. There is an estimated 25% lifetime risk of symptomatic hip OA in people who live to age 85[5], and an almost 10% lifetime risk of undergoing a total hip replacement for end-stage OA[6]. Total hip replacement (THR) is a widely used surgical procedure beneficial to a great many patients suffering from osteoarthritis[7,8]. In 2010, an estimated 2.5 million individuals in the US were living with a THR[9]. By 2030, THR surgeries are projected to increase 71% to 635,000 procedures per year[10]. ***However, hip surgical implants are prone to failure***. Revision surgeries, which are more costly than primary procedures, are expected to exceed 96,000 per year by 2030[4]. The most common reasons for THR revision are hip instability/dislocation and mechanical loosening of the prosthesis[11,12], complications that are implicated in 17.3% and 16.8% of revision THR procedures, respectively[12].

In a study by Ulrich et al over 6 years in 225 patients who underwent 237 revisions, 123 revisions happened due to aseptic loosening (52%) and 37 due to infection (5.5%)[13]. With either of these two the usual solution is revision surgery, at an average cost of $77,851[12]. ***OrthoDx's implanted wireless sensor technology can provide earlier and higher resolution detection of implant movement and lessen the need for revision surgeries.*** Existing clinical diagnostic tools used to identify component loosening are unable to detect real time motion at the micron level, which is when non-surgical intervention would be most beneficial. There are drugs available to enhance osseointegration.[14] With early detection, drug therapy can be instituted at a much earlier stage. The surgeon would have full visibility into the health of the hip implant starting immediately after surgery.

Limitations of Current Approaches: The resolution of standard radiographic imaging is in the millimeter range[15,16,17] and is insufficient to detect initial stages of implant degradation or loosening. More sophisticated scanning techniques, such as magnetic resonance imaging (MRI), bone scans, computerized tomography (CT) scans, are available, but are imprecise at determining quantitative measurements. A literature review of loosening detection by radiography indicated accuracy as low as 66%[3].

The most accurate means for evaluating micro-motion is radio-stereometric analysis (RSA)[18-20]. RSA can measure prosthetic motion shifts with a resolution of better than 100 microns. However, the procedure is costly, involves sophisticated X-ray equipment, requires tantalum beads to be placed in the host bone, involves radiation exposure to the patient and requires expert interpretation. Through RSA, it was found that many components at elevated risk for revision surgery show subsidence of less than 1 mm[21]. Subsidence thresholds of 0.1 to 0.2 mm were also determined by RSA for complications including component loosening and osteolysis[22-25]. In summary, RSA is a sophisticated research technology with extremely limited clinical availability.

Numerous sensor technologies and methods have been developed with the goal of monitoring prosthetic loosening in real time. The most common approach uses vibrometry, a method that distinguishes different loosened states of an implant through changes in vibrational modes[26-31]. However, vibrometry is challenged

by a low signal-to-noise ratio and does not provide a quantitative measure of displacement of the loosened implant. Other strain-gauge-based systems used for "sensor-assisted surgery" can assist with optimal hip or knee implant placement to ensure optimal fit[32-34]. While these technologies could provide an indication of force concentrations at various positions around an implant*, they do not provide direct measurement of implant displacement with respect to the bone, which would indicate loosening*. Further, most of these technologies require incorporation of the sensor within the prosthesis and the delicate mechanism is therefore vulnerable to damage from high inertial forces exerted upon the prosthesis during implantation.

Market Opportunity: Based on approximately 500,000 hip replacements per year, we believe our overall market opportunity will be $300 million per year. We expect our device to sell for $600 per implant (costs to the hospital), where the delivered product will be 3 implantable sensors. After proving the device for use on hip implants, we believe other orthopedic constructs could be easy adjacent markets. After including joint replacements, fractures, spine fusions, wrist repairs and joint reconstructions, our estimated market opportunity is over $2.5 billion per year. An external sensor scanning device and a backend system to collect and manage the data will be sold separately to Orthopedic Surgeons, Physical Therapy Departments, and Manufacturers for use in their offices. Given that there are about 10,000 orthopedic surgical offices and 40,000 physical therapy departments in the US, we expect this service offering to yield over $120 million per year. A subscription service will be offered to manage patient data with the option for companies or clinics to capture and manage their own data on site. The monthly price for this offering will be $200 per month.

Product / Service Offering

- Hospital / Patient
  - Implanted Sensors
- Physician's Office:
  - Sensor Scanning Device
  - Software System to collect and manage data
  - Subscription to manage patient data

Finally, we will target orthopedic device manufacturers with an anonymized data offering based on data collected from our online platform. These data may provide them with critical information for managing and improving their product offerings. Further, it may be useful in bringing new products through clinical trials. We have yet to determine the value of this market, but we believe it to be substantial.

Our approach to the market will be to first establish our product offering through publications and conferences. We will target insurers who will see the biggest cost savings from our technology. Further, insurers will have influence over hospitals and orthopedists (since they will be the direct buyers and implementers of our technology) as they, the insurers, are the end payors.

We will target publications and educational content towards physicians and surgeons as well. Through conferences and publications and direct interactions, we will educate the orthopedic market about the benefits of our product offering. Having a clear picture of movement in the hip would be a game changer for the orthopedist. With full visibility into the health of the hip implant starting immediately after surgery, personalized recovery programs and exact pharmacologic interventions become possible.

The doctors involved in our clinical trials can be our initial connection to influence orthopedists. Through word of mouth and involvement of top-rated physicians, we anticipate building interest in our device. The publications that follow will further help influence the field.

Once we have FDA approval, the primary target of our direct sales team will be hospitals. It is common in the prosthetic market to focus sales efforts directly on the hospitals and their product review boards. Although insurers and doctors will have a say in the process, the use of a specific device is often driven directly by the hospital administration. It will be important for us to set up sales contracts directly with

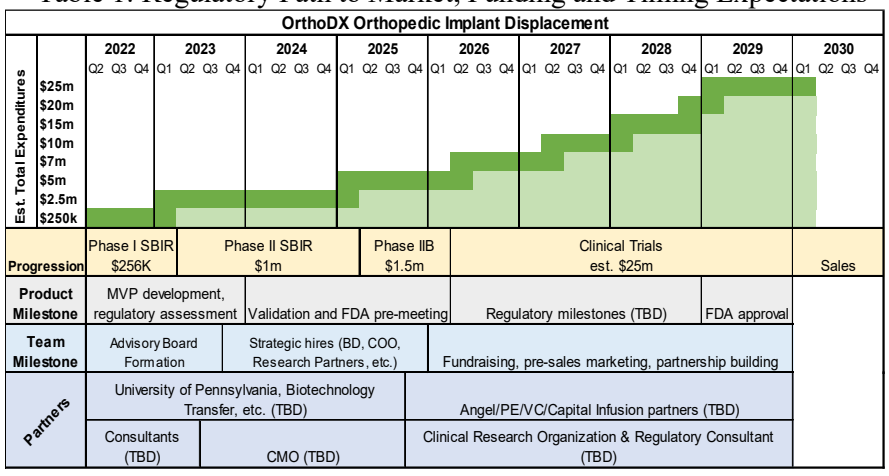
hospitals. Our sales team will focus on building out contracts with all hospitals across the country. For starters, we will target the hospitals where our clinical trials are performed.

A major value to hospitals is tied to value-based care. Because of this, hospitals are at risk of paying for revisions when patients are readmitted for the same treatment or for ancillary conditions related to the treatment. Our system could help hospitals reduce such costs by helping identify patients for remediation within the prescribed post-operative period.

Savings to Health Insurers: The current diagnostic mainstays in the assessment of an implant for possible loosening is an MRI and bone scan. These basic procedures cost $1,699 (using national average cost). Based on the estimate that 1 out of 10 patients will require such a scan, we believe the OrthoDx system presents a cost saving opportunity to the industry of $90 million per year for hip replacements alone. When all other potentially monitored implants are included, the total costs avoided could be as high as $700 million, and this doesn't include savings due to fewer and/or less difficult revision surgeries. A revision surgery currently averages $77,851.

Regulatory Path to Market (Funding and Timing): OrthoDx will use Phase I SBIR (along with Phase II and Phase IIB) funding to develop both a minimal viable product and the initial results necessary to begin discussions with the FDA. The team will identify a clinical development partner and clinical trial partners as part of the research to augment the skills required to undergo FDA clinical trials. Prior to engaging in FDA clinical trials OrthoDx plans to seek necessary skillsets in employees who will help prepare the company for outside investment from angel, private equity, or venture capital funders. The team will, of course, continue to seek non-dilutive capital opportunities alongside external equity investors. Our current team has the expertise in all these areas to ensure prudent and fiscally sound decision making. With conclusion of Phase IIB and after protecting the newly generated intellectual property, OrthoDx will seek to raise the estimated $25m for FDA clinical trials. We also recognize the specificity of skill sets required to make these moves possible and will rely on our team, advisors, and consultants to identify the right individuals to accomplish the fundraising goals required to move to market. In all, we anticipate an 8-year pathway to market assuming our fundraising and partnership development goals are sustained as projected in Table 1.

Table 1: Regulatory Path to Market, Funding and Timing Expectations



3. The Technological Solution

OrthoDx has developed a system (Patent US 10,980,419) that enables early detection of prosthetic implant loosening. Our implantable wireless sensor system will measure motion of prosthetic implants at the micron level, helping detect pathologic loosening and enable early intervention to correct the problem. The

advantages of our proposed eddy current sensor include simple structure, low cost, small size, long life, insensitivity to dielectric medium, and micron scale resolution[35].

OrthoDx technology uses *in vivo* inductive proximity sensors as a practical and novel approach to precise measurement of orthopedic implant micro-motion. A simple tank circuit consisting of a coil and capacitor is securely affixed to the surrounding bone within a few millimeters of an implant to form an electromagnetically coupled system. To make this possible the implant must be capable of conducting electricity. The great majority of implants today are made of conductive materials. (If made of non-conductive materials such as ceramic, a conductive area may be imbedded or plated upon the implant to make it compatible with our system.) An external antenna driven by a controlled power source generates a specifically addressed brief wireless transmission which passes through the intervening soft tissues and bone and excites the sensor's LC tank circuit into oscillation at its resonant frequency. The distance between implant and sensor affects the damping rate of the sensor circuit oscillation because coupled energy is lost in the implant due to eddy current dissipation. The closer the implant is to the sensor, the greater is this damping effect. These proximity effects occur in the near field. The power involved is far too small to produce any measurable thermal effects. The WCM's external antenna monitors and collects data about the field emitted by the sensor as it responds to the initial excitation. OrthoDx's algorithms process this data to extract high resolution proximity information. Depending upon the resting distance between the implant and the sensor, micro-motion specificity better than 20 microns can be reliably achieved.[36]

This basic principle of operation is well understood. Our application of these physics is novel. Our proprietary circuit and signal processing algorithms extract precise high-resolution measurements from miniscule signals hidden within much higher amplitude raw data that can be quite noisy. With our technology these measurements are substantially invariant against changes in the position of the external antenna with respect to the patient and can be made without compromise to accuracy while the patient is moving and in the presence of normal blood flow and pulse.

Comparison to the current gold standard: RSA has been used for decades primarily as a research tool to forecast the survival rates of various implant designs. In cementless fixation, there is evidence that the amount of acceptable early migration should be small and less than 1 to 1.5 mm within 2 years to avoid early and midterm revisions.[37,38] But RSA is unable to provide real time motion measurements without sophisticated x-rays.

RSA involves the insertion of many small beads of tantalum into the bone surrounding the implant to function as markers. This insertion process and gaining access to the bone to do it will increase the surgical burden of the implant surgery. We expect the process of mounting a single OrthoDx sensor per each monitored site will be significantly simpler and easier to achieve. Placement of each sensor will take no longer than a routine screw placement, a matter of a few minutes.

The complex process of obtaining RSA studies involving patient inconvenience, x-ray exposure and multiple expenses, constitutes a significant impediment to collecting prosthetic motion data. In contrast, the OrthoDx system allows the physician to monitor the patient as frequently as desired, gathering data with micron precision from day one of surgery throughout the lifetime of the prosthesis, using portable equipment, an uncomplicated process and with no x-ray exposure.

Research on the efficacy of pharmacologic intervention to slow down or stop osteoclastic activity to avoid the need for revision surgery secondary to aseptic loosening is progressing. By monitoring and evaluating motion within 20 microns, the efficacy of drug therapy on induced osseointegration can be carefully monitored.[39] This is applicable to both a research and clinical setting. If OrthoDx can help bring easy simple, reliable real-time measurements to bear on this challenge an estimated financial burden of some 8 billion dollars in annual expense can possibly be lowered and patient outcomes can be generally improved.

In summary, the key features of our system include:

- Micron scale resolution (target = 20-micron resolution at 5mm distance from the implant),
- Full three-axis measurements to capture all components of implant motion and to discriminate between implant "loosening" *vs*. the intrinsic flexural motion of the bone-implant structure
- Low-cost, low-hassle, advanced non-radiographic electromagnetic proximity measurement that obviates expensive, radiation-exposing imaging equipment
- Non-contact, non-vibrational measurement technique for detecting motion that is compatible with existing structural implant products and requires no modification of the prosthesis
- Sensors are implanted separately, allowing precise placement with minimal insertional trauma to the sensor
- Sensors are durable, use no complex electronics or fragile components, and will easily withstand mechanical shocks and stresses attendant to seating the implant during surgery.
- Versatile technology can be translated for a range of orthopedic procedures, including other types of implants, spinal fusions, and fracture care
- Sensors are dormant until addressed by a specific externally generated electromagnetic field. No internal battery or other power source
- Though sensors must be affixed to the host bone securely, the actual technical requirement is only that each sensor remain stable in relation to the host bone for the duration of a single measurement sequence. (a few minutes.) Long term migration presents a problem only if the sensor migrates too far from the implant or if it collides with the implant.

Key Technical Challenges and Market Risks: Our risks in getting this product to market lie in these key areas:

- FDA Approval: Although we feel we have made a strong initial assessment of our regulatory path, acceptance by the FDA will be the most critical step in obtaining market traction. Given that we are inserting a foreign device into the human body ideally for the lifetime of the patient, we will need to show that the device is inert, doesn't create infections and doesn't cause fractures. We will outline strategies to overcome these technical risks. (See "Objective 3. Sensor Enclosure and Fixation Design" below.) Further, we'll work closely with regulatory advisors to maximize our chances at achieving FDA approval.
- Hospitals: The hospital is the entity that will write a check for our technology. Their buying decision is heavily influenced by the insurers; however, hospitals see no direct value for this device other than extended surgery time to implant the sensors and their markup of the price of the sensors themselves. Therefore, we will rely heavily on a trained salesforce as well as demand from insurers to convince hospitals to use the device. Additionally, the transition to value-based care in the US healthcare market will demand continued innovation from hospitals and providers to reduce the need for readmission for procedural errors most of which will not be compensated for by insurers.
- Orthopedists: Although orthopedists we have interviewed love the device for the information it can provide, they tend to be tight with money. There is also a desire among doctors to work with existing technology versus change to something new. Given that new skills will be required to implant the sensors, we will have to focus on proving our technology's value to overcome this potential market risk.
- Orthopedic Device Manufacturers: Our device could potentially show which joint replacements are effective and which are not as effective. Therefore, some manufacturers may attempt to block our market acceptance given the potential of our product to show that their device is not as effective as they claim, while those with a superior product may welcome us. Again, we will focus on the value to the insurers and positive reviews from doctors to overcome this market risk.
- Insurance Companies/ Providers: Our Market acceptance will be driven by the potential of large cost savings made possible by early detection of pathologic component loosening.

- Technical: Encasement of sensor within biologically inert casing; Casing must withstand torque pressure of affixing to bone; Casing must be solidly attached to bone; Concomitant readings of multiple sensors present a challenge due to potential sensor crosstalk.

4. The Company / Team

Dr. John Lucey, Founder and CEO of OrthoDx and former orthopaedic surgeon, will serve as the PI of this grant, overseeing all the project components and making sure all the milestones are being met in a timely manner. **Mr. Paul (Vo) Ierymenko**, Senior Developer at OrthoDX, having already successfully built a vertical axis micro-motion detection prototype, will develop the 3D-enabling motion detection across three planes described in Objective 2. **Dr. Michael Hast**, Director of the Biedermann Lab for Orthopaedic Surgery at the Perelman School of Medicine, University of Pennsylvania, will serve as a consultant to the project. Dr. Hast is a Biomechanics and Performance of Orthopaedic Implants expert and as such he will serve as a consultant to this project and carry out the cadaver testing study described in Specific Objective 3. **Dr. Cynthia Pritchard** will serve as a consultant and provide regulatory expertise as the company progresses toward a pre-IDE meeting with the FDA. The OrthoDX team will work side-by-side to coordinate scientific and project management objectives. Continuing an established practice, the PI and Developer will conduct bi-weekly video conferences to discuss the progress of studies. In addition, Dr. Lucey will conduct weekly teleconferences with vendors to discuss progress, address potential issues and plan for the next quarter. Finally, OrthoDX will communicate with the FDA to schedule an initial pre-IDE meeting to discuss endpoints and identify further studies required for the IDE.

OrthoDX is focused on the delivery of a novel, low cost, long life sensing modality to address the complications of tracking all procedures requiring monitoring the stability of a construct (i.e., all joint replacements, spine fusions, fracture care, arthrodesis, joint reconstruction, etc.). The company founder and the principal investigator for the project, John Lucey, Founder, Orthopedic Surgeon, initiated the motion sensor project in earnest shortly after his retirement from clinical orthopedic practice. Having managed well over one thousand patients with total hip replacement, he clearly saw the need to have a more precise measurement of implant micro-motion. Upon retirement from practice Dr. Lucey immediately began working towards the effective motion detection system that OrthoDx is now developing.

Paul Vo (Ierymenko), a professional inventor, will also support the team on this project. Vo holds several patents and has a long history of innovation and product development starting in 1994 at QSC Audio Products where the company brought him in to develop what became for a time the world's most powerful audio amplifier. (9000 Watts.) As Director of R&D and CTO his team's product development and R&D efforts helped QSC grow to a $100M full-service manufacturer with a strong lineup of amps, signal processing, digital audio distribution and installation loudspeakers. He is also the inventor of the patented electromagnetic string vibration control technology behind the legendary Moog Guitar and the Moog Lap Steel, the Vo-96 Acoustic Guitar Controller, and the hand-held "Wand". His electromagnetic motion control technology makes possible a new form of music synthesis, sound synthesis achieved through precise computational control of individual harmonics in any physical medium capable of vibrating to generate sound.

With the expertise of John Lucey, Paul Vo, and the assistance of researchers at RTI, NC State, Western Carolina University, OrthoDx has reached the stage of having developed a prototype that clearly demonstrates our system, a published paper (IEEE)[40], and a patent (US10980419)[41]. The founder has invested over $450K into the company since its inception. We have approached the motion problem in a way that allows for universal application of our sensors, provided they are interacting with an implant having a conductive surface. Most implants are made of electrically conductive metals so there is no need for modification of the implant. Our system is compatible with virtually all implants in use today.

The founder is aware that a vibrant, knowledgeable team is necessary to fully develop this technology. We believe the expertise of our present members as well as the full-time commitment of the founder will allow us to reach the stage of product development capable of initial review by the FDA. After this step, decisions will be made as to licensing of our technology or pursuit of full-blown corporate development. We have identified personnel for the latter.

We have arranged with Meraqi Medical to encapsulate and test the sensors. Paul Vo will develop the three-dimensional capability of the sensor system. Cadaver testing will be accomplished through the Biederman Orthopedic Laboratory at the University of Pennsylvania.

Other team members include: William Cardine, Financial Officer; Cynthia Pritchard, FDA Consultant; Thomas Roberts, General Counsel; Laura Kelley, Esq., Patent Attorney, Myers Bigel; RTI International, Engineering Consultants - David Dausch, Meghan H. Craver, Jim Carlson, Edward Grant, and Hamed Mohammadbagherpoor.

Potential Collaborators include: University of Pennsylvania, Imperial College of London, Meraqi Medical

5. Technical Discussion and R&D Plan

Components of the OrthoDX System: OrthoDx's clinical system includes multiple in vivo Micromotion Sensors (MMS) and an external Wireless Communications Module (WCM) for powering and communicating with the sensors via near-field wireless radiofrequency (RF) coupling (**see Figure 1**). The heart of the system is the MMS, (Figure 2), which consists of an inductive sensor coil, a ferrite core and a special capacitor. The MMS serves three essential functions: (1) receiving power from the wireless interface, (2) communicating data back to the interface, and (3) measuring the distance to the implant. Measurement resolution is inversely proportional to the coupling distance between the sensor and the prosthesis and directly proportional to sensor diameter. The MMS in our existing prototype is 10 mm in diameter for placement in the femoral canal, but MMS diameter shall be scaled down to 5mm for our three-axis system. Based on prior literature, we established a minimum target resolution of 100 microns of implant displacement at a 15 mm sensor-to-implant distance. Evidence suggests that this resolution is required to detect early implant loosening. At 5 mm distance from MMS to implant the resolution improves toward 20 microns and such placement is possible in the greater trochanter area.

Figure 2. The MMS

The Wireless Communication System, (WCM): Each location where patients are monitored must have at least one WCM system. Our prototype WCM employs wireless power transmitter and data transceiver hardware of novel design. To facilitate multi-axis motion sensing we will expand on this by incorporating an electronically oriented field antenna into the WCM for transmitting power to and exchanging data with one or more MMS. Such an antenna may be 10 inches in diameter. In use, the WCM may be on a flexible arm anchored to a stand and the antenna may be attached to the patient with a waist band and a band around the thigh. The WCM antenna should be positioned as closely as practical to the location of the patient's implanted MMS sensors. A microcontroller shall run software controlling the wireless power and transceiver hardware of the WCM. As shown in Figure 3, the WCM antenna shall consist of three mutually orthogonal antenna coils. The microcontroller shall drive these coils with similar signals differing in amplitude and phase to generate a field of any arbitrary spatial orientation. Thus, no matter the relative rotation of a particular MMS to the WCM antenna, the WCM can rotate its field to the best coupling orientation. The WCM also communicates over USB to any familiar and suitable general-purpose

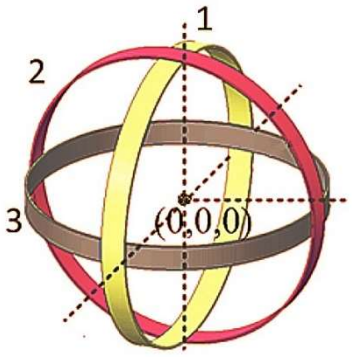


Figure 3. The Electronically Oriented antenna of the WCM

computer which shall run OrthoDx software instantiating a user interface for receiving commands from a clinician. This software shall also process and store data and will display parameters and measurement results for clinical evaluation. The general-purpose computer may be equipped with conventional Wi-Fi and an internet connection making data sharing and cloud storage possible, etc. The general-purpose computer may be an OrthoDx branded machine having features specifically useful or appropriate for clinical use.

Clinical Scenarios: Figure 4 illustrates the proposed clinical process of measurement, analysis, and evaluation of implant loosening. The subject's femur is equipped with at least one MMS, and this sensor is coupled wirelessly to the WCM. The subject alternately loads and unloads the leg with their body weight. This may be accomplished by walking in place or merely by shifting weight from one leg to the other. The OrthoDx system records a sequence of continuous measurements during several cycles of loading and unloading the leg.

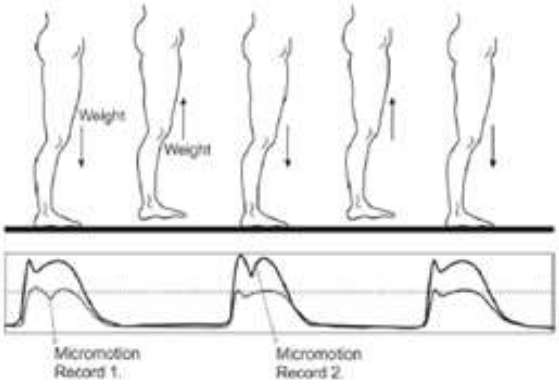


Figure 4. Clinical method where measurements are taken while loading and unloading the leg.

An implant beginning to loosen will exhibit increasing micro-motion well before there is obvious bone degeneration. ***A new recording of the same subject (timing prescribed by the orthopedist) is compared to a recording made during a previous test. If this comparison reveals that the implant's micromotion with respect to the femur is increasing when it should be decreasing as recovery progresses, we have a powerful and early clinical indication of implant loosening***. Similarly, after full recovery we would expect to see the amount of motion remain stable. If a subsequent measurement showed increased implant motion with respect to the host bone, this would be an early indicator of a destabilizing implant.

With our system, patient monitoring may begin immediately after surgery. Measurements are taken at regular intervals throughout the course of therapeutic exercises. During a typical exercise session, measurements are made continuously while loading and unloading the leg with a specified weight or exercise device, e.g., stepping on a scale. As the supporting bone grows into the implant, such ongoing measurements of the ensuing clinical progress are expected to reveal a gradual decrease in the displacement of the implant relative to the femur in response to load. An unexpected reversal of this trend would alert the therapist to potential problems and may indicate changes to physiotherapy, for example delaying the application of full weight bearing so as not to compromise osseointegration. With the matter resolved, subsequent checkups should then show a continuation of implant integrity. Our system will provide data for such insights. Physiotherapy could be tailored to each patient to produce more uniformly successful results.

Long-term monitoring should continue indefinitely on a relaxed but regular schedule, perhaps monthly or quarterly. With the patient's individual measurement history as a baseline, our system would detect implant loosening at the micron level by flagging any increase in implant displacement relative to the femur in response to a given change in the load supported by the patient's leg. Such monitoring could identify later stage problems earlier than current technology allows, likely before the patient experiences pain and other symptoms of implant failure. Remedial measures are best performed before the remaining bone is damaged by the action of a loosened implant or osteoclastic activity.

Please note that in the scenarios outlined above, our system does not depend upon the existence of a large data set compiled from multiple patients. This makes the OrthoDx system tactically superior to any

competing system that requires the accumulation of a large and diverse set of patient data before its measurements can be interpreted in a clinically useful way.

Our system is expected to be clinically useful with the very first patient to receive our sensor implant. It requires only the patient's own ongoing measurement data as its baseline to identify and display a positive, benign, or negative trend in how the patient's implant behaves under changing loads. Of course, much may be learned over time through collecting case data from a large and diverse population of patients, but with our system this is a bonus, not a requirement.

Our Current Development Status: To date, we have optimized the sensor coil using COMSOL software and verified that the design can gather proximity measurements at micron-scale resolution with the MMS positioned at realistic distances from an implant. **We have a functioning single-axis prototype capable of detecting prosthetic position shifts within 20 microns with a sensor prosthesis distance of 5mm**.

Optimization of sensor coil design. In collaboration with RTI International, and using COMSOL software and finite element analysis, we designed and simulated the functioning of the MMS[40]. We created three-dimensional models for two coil designs (reproduced below is Fig. 5 from our 2019 peer-reviewed publication[40]): a wire-wrapped solenoid coil with 45 layers using 35 AWG gauge insulated magnet wire, and a 4-layer circular flat spiral coil, simulating a coil on a printed circuit board. A cobalt-chromium metal rod (9 mm diameter) was included in the model to simulate the femoral component of a metal hip implant. We analyzed each coil at different resonance frequencies and implant displacements, modeling the MMS, EM field, skin effect, coupling between windings, and series resistance. The solenoid coil resulted in higher resolution and range for detecting implant loosening. Note: We have recently determined that results are

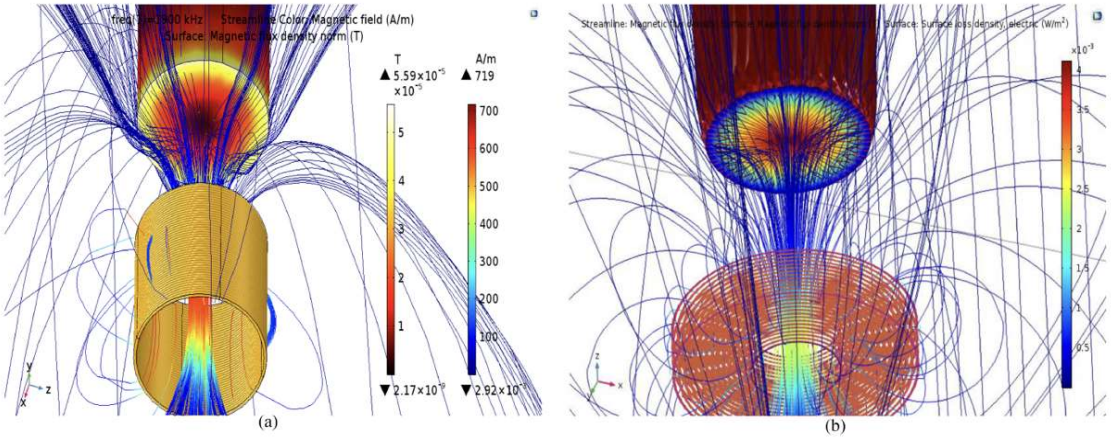


Fig. 5 3D proximity sensor simulation (a) Solenoid coil (b) Circular flat spiral coil. An electrical current of 25 mA was applied to the solenoid coils which generated the magnetic field (blue lines) shown and interacting with the metal implant.

remarkably similar when any electrically conductive metal is used in the implant, and ***we have verified titanium and cobalt-chromium***, as well as copper, stainless steel, iron, and aluminum. Our measurement technology is intentionally designed to rely only on electrical conductivity.

Effect of variations in the solenoid coil geometry: To optimize the implanted sensor design and to ensure its capability of motion detection, the solenoid coil was modeled and analyzed for a variety of geometries. Solenoid coil geometry influences the amount of energy dissipated by the implant, eddy current generated on the implant surface, and ultimately, the size of the sensor[40]. The six solenoid coils modeled had different numbers of turns (45 vs. 15.5), numbers of layers (one vs. two), and presence or absence of a ferrite core to increase magnetic flux. The Co-Cr rod was placed at 11 mm distance from the coil to approximate an implant. Electrical currents at desired frequencies were applied to the coils in COMSOL, and the resulting quality factor (Q, a change in which translates to the ability to detect changes in the distance from the rod

to the sensor), induced current, and power dissipation to the Co-Cr rod were calculated. *Sensor coils with a ferrite core induced more magnetic energy on the simulated implant and had greater sensitivity than the coils without the ferrite*. Coils had higher Q and induced greater current/power dissipation at 1900 kHz resonance frequency compared to 1074 kHz, indicating increased sensitivity and better coupling with the Co-Cr rod. Dielectric losses are known to increase with frequency, which is a factor in selecting the MMS frequencies.

Effect of blood and bone on hip loosening detection: The MMS was tested for performance in different media (*i.e.*, air and biological materials such as blood and bone). Simulation results showed that sensor coils gave similar results in air, or bone and blood. Equivalent results were obtained with physical experiments, where a conductive saline solution and acrylic tube were used to emulate blood and bone, respectively.

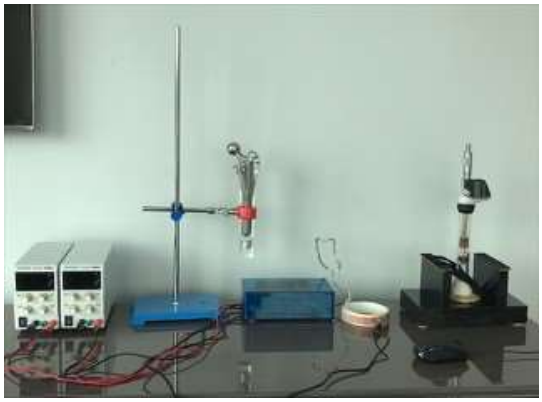


Figure 6. From left: power supply, acrylic model of femoral prosthesis, wireless communicating module (WCM) with external antenna, titanium rod affixed to adjustable micrometer, sensor (MMS) situated 10 mm from tip of titanium rod

Verification in a benchtop experiment. Using the results of the COMSOL simulation, we fabricated a physical MMS for benchtop testing. We mounted the sensor coil on a printed circuit board (PCB) and soldered the wire leads to PCB traces leading to an SMA (coax) connector. We mounted the parallel tank capacitor on the underside of PCB, in parallel with the inductor coil. The SMA cable was attached to an LDC 1101 board that measured the MMS parameters. The 10 mm Co-CR rod (ASTM 1537) used to model the implant was mounted to a translation stage manipulated by a manual linear actuator with 25 micrometer resolution accuracy. The sensor was analyzed with and without a ferrite core, in air and phosphate buffered saline (to approximate blood), and at 1074 and 1900 kHz resonance frequency. *We found that with ferrite and at 1900 kHz, the sensor would detect movement at high resolution (25 µm) over a range of fixed distances from the implant (3 mm-8.5 mm). The sensor's sensitivity was not affected by immersion in saline*.

Our preliminary findings confirm that our optimized sensor coil can detect implant movement with remarkably high resolution across biologically relevant distances in a simulated biological environment.

Phase 1 Research Plan: A limitation of our current prototype is that it addresses only a single sensor and is therefore capable of detecting motion of an implant in a single axis only. We will enhance the system to enable it to sense motion across 3 axes. Additionally, we will modify the sensor design through modeling tools using our contractor and sensor expert Meraqi. The results of Phase I will 1) prove the ability to detect motion in three dimensions, and 2) establish a sensor design ready for full development in Phase II. These are the milestones we will pursue in this Phase I SBIR project. The primary objectives of this Phase I SBIR project are thus to (1) enhance the system to generate a 3-D construct of implant motion, (2) test the resulting system in a cadaveric model, and (3) develop implantable sensor design for further development in Phase II.

Objective 1. Enable 3-D detection of implant loosening. This Objective will be carried out by Paul Ierymenko and take approximately 9 months overall. To enable 3-D motion detection, at least three MMS devices must be deployed in suitable locations and at mutually orthogonal angles that will likely differ slightly from patient to patient. To address these sensors regardless of their angle of orientation we will develop an electronically oriented antenna, transponder and firmware to discover and align the antenna field with each sensor's orientation.

Objective 1.1 Develop a suitable electronically oriented antenna, electronics and software. The antenna will be constructed of wire wound coils; its substrate form shall be rigid, round, featureless, non-metallic, non-ferrous and with low dielectric loss. We will assess coils ranging from 4 inches to 10 inches in diameter. The coils shall be wound of 14-gauge magnet wire. We will also test coils constructed such that each course of wire is composed of several parallel smaller gauge wires such as 24 AWG, as this may improve the Q-factor of the coils making them better receptors.

Construction procedure: Double backed foam tape will be applied once around a circumference of a round "ball" coil form. The tape must be wide enough to provide an adhesive foundation for a single layer of 10 to 20 closely wound turns of magnet wire. The coils are hand-wound. The first coil is wound upon this path around the ball, laying and adhering the wire to the circumferential adhesive foam foundation. Enough turns of wire calculated to produce 10 uH of inductance will be applied. Two more such adhered coils will be wound in a mutually orthogonal arrangement around the ball coil form. The resulting WCM antenna may be wrapped in self-sealing silicone tape to further secure and insulate the windings and connections and seal away any exposed adhesive areas of the foam tape.

Interface Electronics: Each of the three coils of the WCM antenna will be driven by a custom electronic circuit of a similar design to that used in our existing single-coil prototype. Each drive circuit will consist of a computer controlled arbitrary waveform generator and a driver stage capable of imposing a high voltage waveform in short bursts upon its associated coil. The frequency range of the driver will be between 1.6 MHz and 15 MHz and the amplitude will vary between 20 and 1000 volts. This large voltage range is to compensate for wide variations in the distance between the WCM antenna and the MMS different patients may present. Each coil circuit will have electronic switches to toggle the coil between the driver and a buffer stage for monitoring and amplifying signals received by the coil. The three sets of signals will be simultaneously digitized by a suitable multichannel digitizer, each independent channel having a resolution of 14 to 24 bits and a sampling rate of at least 100 MHz.

Verification of proper Antenna and Interface Electronics Function: Since the hardware described above is designed to be controlled by a software program, its operation will be verified in tandem with development of the custom software. This is basic to the creation and debugging of such a system. The expected waveform generated by the software will be routinely verified by oscilloscope channels connected across the coils. Similarly, signals from an addressed MMS can be viewed by an oscilloscope at the MMS and verified by comparing to the screen output of the software.

Objective 1.2. Test the system. An apparatus will be constructed, having at least three MMS sensor devices firmly configurable within a 15-degree range of 90 degrees to one another and with each having individual associated means to move a titanium rod serving as an electromagnetically representative prosthetic implant in increments of 1 micron. The proposed apparatus (based on an existing set up; see **Fig. 6** above.) would have three such features mounted on a frame and in close relation to one another, with the MMS devices approximating the positions they will be in when deployed within a femur. The system is exercised in a manner simulating an actual clinical measurement of a human subject. A series of measurements are taken under control of the software as the three titanium rods are manually adjusted closer or further from their associated MMS by a precise number of microns predetermined for the test. Having three titanium rods that are adjustable will allow for precise assessment of each plane of motion (i.e., x, y, z planes). Then we will change the relative angles of the MMS positioning components to simulate differences between where the sensors are placed for different patients. The operative success of the system is verified when the readings provided on the computer screen by the custom software match the actual measured displacements of the rods relative to the MMS sensors per the milestones below.

Milestones: ***Match or exceed the performance of our current prototype, which can detect 10 microns of change at 2.5 mm distance, 40 microns of change at a 5 mm, and 100 microns of change at 10 mm distance.*** Show that these numbers are achieved in the context of multi-axis measurements.

Potential Challenges and Alternative Approaches: For multi-axis monitoring several MMS sensors may be deployed at different angles and positions along the femur. Extracting isolated measurements from each MMS without crosstalk with other nearby MMS sensors presents a challenge. One solution is to pre-assign a unique operating frequency to each MMS, activate them all at once, and process the composite data to differentiate each MMS according to its unique frequency. This method would be the fastest because all points are measured at the same time. **Alternative:** If experimentation shows this does not provide sufficient isolation to maintain measurement precision, we will instead choose to add circuitry to each MMS. This circuit shall activate its MMS upon reception of a unique command from the WCM. Each MMS sensor would thus be activated one at a time in sequence. This method definitively solves the isolation challenge but at the cost of increasing the time needed to complete a full measurement assay of a patient. This increase is negligible, being one additional measurement interval for each additional MMS sensor and likely amounting to less than one extra minute for the patient.

Objective 2. System verification in a human cadaveric model. We will verify the system in a human cadaveric model at the University of Pennsylvania Biedermann laboratories. The model will consist of rigidly fixed cadaveric femora prepared to accept three MMS sensor plugs containing a wire coil with ferrite core. These will be placed in a mutually orthogonal arrangement in the greater trochanter area of the femur. A titanium femoral prosthesis attached to a multi-axis servo driver will be exercised through various motions representing a variety of loosening implant behaviors.

Experimental design: We will first conduct bench model testing to verify system performance in a simulated human femur, which will be used to identify baseline measurements for a subsequent analysis in the femur of a human cadaver. We will anchor the prepared simulated femur to a testing workbench to minimize motion and system background noise. A titanium prosthesis will be inserted into the femur. We will implant the sensors into the femur using acrylic cement or suitable alternative. The implant shall be rigidly secured to and driven by a multi-axis servo system that will oscillate the implant through a series of micron-scale motions in a series of cycles repeating at 40 beats per minute. This will emulate a patient's gait and the possible effects of loading and unloading the implant in the course of walking. Our three-axis prototype system will display these motions and their relevant statistics as they occur.

Once satisfactory data is obtained with the simulated femur model, the same approach will be applied to secure and test the system in a human femur, male and female, and surrounding tissue included in a cadaver hip and leg section.

Milestones: Verify that sensor measurements are within 50 micron of the bench (ground truth) measurements of the sensor and prosthesis.

Potential Challenges and Alternative Approaches: Background noise could be an issue in obtaining sensor measurements, especially when data from all three sensors are simultaneously collected. Collecting sensor information in sequence can overcome this issue. Given that sensor collection happens in milliseconds, sequential collection should not be a problem. Most of these issues should be addressed in Objective 1, due to the fact that sawbones are similar to fresh cadaver bone.

Objective 3. Sensor Enclosure and Fixation Design. Encapsulation and formal characterization of our sensor will be performed by Meraqi Medical, a world -wide leader in medical plastics fabrication.

A- The MMS sensor must be biologically inert. The inner inductive coil, capacitor, and core shall be surrounded (potted), within a suitable nonconductive, biologically tested plastic such as PEEK.
B- The exterior surface of the MMS sensor must be suitable for rigid fixation to either cancellous or drilled and tapped cortical bone.
C- Lifetime of the devices will be characterized through accelerated aging in saline.

Following discussion of product requirements, a preliminary enclosure will be designed. There are many available sources to model our prototype. The push lock sensor system advanced by Van Arkle[42] is attractive. To this anchoring system, or one of similar design, will be added a capsule containing the coil and capacitor which comprises our sensor. There will be two methods of manufacturing to explore:

1) Method 1: PEEK over mold of the electronics. This path will require welding and high temperature components to withstand the temperatures and pressure during PEEK injection molding. Soft tooling (aluminum) can be used to reduce cost.

2) Method 2: Machining a PEEK enclosure sealable with an ultrasonic weld. This path will design a two-part enclosure with features required for ultrasonic welding. The electronics will be placed inside, the interior will be potted with epoxy and the enclosure welded shut. Tooling is required for the ultrasonic weld.

Meraqi will produce formal validated specifications for the MMS. Examples: Accelerated aging to understand the effect of moisture ingress. Benchtop force measurements to understand how much force can be safely applied during insertion and anchoring/withdrawal of the implanted sensor.

Milestones: Benchtop testing to verify that new sensor can detect 10 microns of change at 2.5 mm distance, 40 microns of change at a 5 mm, and 100 microns of change at 10 mm distance after suitable coating and torque applications.

Potential Challenges and Alternative Approaches: Although we believe a PEEK enclosure will work effectively, there could be something better. Dozens of off-the-shelf coatings exist and will be explored.

Rigor and Reproducibility: Various practices known to be effective will be employed: 1) successful replication; 2) proper controls; 3) statistical analyses; and 4) anonymized sources during data analysis. To address SABV, we will use both male and female femurs/bones for the proposed studies in Objectives 1.3 and Objective 3.

Summary and Timeline: These milestones represent a significant step forward in our system's technical development and set the stage for *in vivo* and biocompatibility testing in a Phase II project.

Objectives	**Months**		
	1-3	**4-6**	**7-9**
1. Developing 3D detection			
2. Cadaver testing			
3. Sensor Design			

Table 2. Phase I proposed timeline.