SUMMARY STATEMENT

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(Privileged Communication)

Release Date: **06/29/2018**
Revised Date:

Application Number: **1 R42 AR074853-01**

Principal Investigator

BEHZADI, KAMBIZ

Applicant Organization: BEHZADI MEDICAL DEVICE, LLC

Review Group: **ZRG1 SBIB-Y (12)**
Center for Scientific Review Special Emphasis Panel
Cardiovascular and Surgical Devices

Meeting Date: **06/14/2018**
Council: **AUG 2018**
Requested Start: **12/01/2018**

RFA/PA: **PA18-575**
PCC: **3 E**
Dual IC(s): **EB**

Project Title: **Automatic Intelligent Prosthesis Installation Device (AIPID) for joint arthroplasty that predicates impaction of implants on the stress response of bone**

SRG Action: **Impact Score:31**

Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**

Human Subjects: **10-No human subjects involved**

Animal Subjects: **10-No live vertebrate animals involved for competing appl.**

Project Year	Direct Costs Requested	Estimated Total Cost
1	212,607	229,708
2	859,191	928,300
3	207,043	223,696
TOTAL	1,278,841	1,381,704

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R42AR074853-01 Behzadi, Kambiz

RESUME AND SUMMARY OF DISCUSSION: In this fast track STTR application, the investigators proposed to develop an automatic press fit fixation mechanism (AI-PID) for Total Hip Replacement (THR) procedures. The Study Section agreed that the proposed research and development addresses a significant problem since the current methods for press fit fixation are primarily qualitative, are not standardized, and are subject to great variability, especially for the less-experienced surgeons. The Strengths of the application include the identification of a significant clinical problem in THR procedures; an experienced PI in expertise of orthopedic surgeon; the strong supporting team with expertise relevant to the project; the innovative proposed work with the well-suited approach to test the research hypothesis and a great deal of preliminary data based on phantoms and preliminary bone experiments support the idea of making these measurements; the excellent environment for proposed work. In addition, the project milestones, scientific and statistical methods, expected outcomes, and potential problems are clearly identified and adequately addressed. During the discussion and in the written critiques, the reviewers raised their concerns including the unclear that the proposed device can be fabricated and make the necessary measurements; the unclear that these measurements alone can improve outcomes when measured at the time of implantation; the unclear what level of pressures and sensitivity are required to obtain useful data. Overall, the Study Section remain the enthusiasm of this application considering that this proposal has significant potential to bring a very useful orthopedic tool to the marketplace.

DESCRIPTION (provided by applicant): Currently, over 400,000 total hip replacement (THR) surgeries are performed in the US each year, the vast majority of them utilizing press fit fixation. Successful seating of the implant requires a delicate balance between seating the implants deep enough to obtain sufficient primary stability, while avoiding fracture of bone. Inadequate stabilization may lead to aseptic loosening, while over stuffing the prosthesis may lead to fractures. However, current methods used to achieve press fit fixation are primarily qualitative, are not standardized and subject to great variability, as surgeons in general do not have the proper tools to produce consistent results. Moreover, the optimal endpoint of press fit fixation has not been able to be clearly defined. Consequently, surgeons must rely solely on their qualitative proprioceptive senses to determine optimal press fit fixation. A system and method is needed to quantitatively accomplish the optimal press fit value for any implant/bone interface, regardless of the variables involved. To address the above deficiencies, we are proposing a novel means of accessing and processing various force responses of bone. Based on experiments that we have performed, simulating impaction of an oversized acetabular prosthesis into an undersized bone substitute cavity, we have developed the Invasive Sensing Mechanism (ISM) concept, which hypothesizes that a point or small range exists, constituting a best fixation short of fracture (BFSF), which should serve as the optimal endpoint for press fit fixation. We propose to develop an Automatic Intelligent Prosthesis Installation Device (AI-PID) to enable optimal press fit fixation through its ability to assess the stress response of bone at the implant/bone interface and predicate application of force, in a controlled, quantifiable and incremental fashion, on this value. Based on measurement of the relevant impaction forces, cup insertion, and number of impacts to full seating, this instrument will direct a binary decision guiding orthopedic surgeons regarding whether 1. impaction should continue, and if so, whether 2. applied force should be increased or stay the same. In order to define the requirements and prove the feasibility of our approach, Phase I will involve validation of the ISM concept, where drop tests will be performed in a simple test stand and impaction models, and the relationship of all the forces at play during implant insertion will be evaluated. The ability of ISM to reliably determine the BFSF endpoint will be confirmed in four specified implant/bone substitute systems. Phase II will involve development and testing of an AI-PID instrument with the following features: 1) ability to deliver precisely controlled axial impacts of known impact energy, 2) ability to increase or modify applied force during use, 3) ability to measure the relevant impaction forces, 4) ability to automatically control the application of impact energy to optimally seat an acetabular cup

using the algorithms determined in Phase I, 5) communicate data pertaining to ISM and BFSF to the surgeon, 6) allow for manual override and selection of impact energy by the surgeon.

PUBLIC HEALTH RELEVANCE: Hip replacement surgery requires a delicate balance between inserting the implant deep enough to maintain sufficient grip, while not too strongly such that it places the patient at risk for fracture. However, current methods used for such surgery are primarily qualitative – with the surgeons relying entirely on their own senses and intuition – are not standardized, and subject to great variability, as surgeons in general do not have the proper tools to produce consistent results. We are proposing to develop an instrument and a method to reliably apply the correct amount of force, based on measurements that the tool will perform on the implant, the bone, and itself, in order to guide the surgeon as to whether they should continue inserting the implant, and if so, whether they should increase the force applied or keep it the same.

CRITIQUE 1

Significance: 1
Investigator(s): 2
Innovation: 1
Approach: 2
Environment: 2

Overall Impact: The proposed research and development addresses a significant problem, as more than 400,000 total hip replacement (THR) surgeries are performed each year in the U.S., with documented failure rates ranging from 25% to 50%. Many of these failures can be related to difficulties in assessing optimal implant stability: implants must be seated deep enough to obtain sufficient primary stability and prevent aseptic loosening, while avoiding fracture of bone. Current methods for press fit fixation are primarily qualitative, are not standardized, and are subject to great variability, especially for the less-experienced surgeons who perform 80% of such procedures. Moreover, the optimal endpoint of press fit fixation has not been able to be clearly defined. There is clearly a need for advanced surgical technologies that can quantitatively accomplish the optimal press fit value for implant/bone interface, regardless of the variability, and provide a quantitative surgical endpoint for these THR. If successful, the proposed technology could significantly impact surgical practice and improve patient outcomes. The project involves an 18-month Fast-Track STTR plan of R&D: Phase 1 (months 1-6) builds on impressive prior work and focuses on more extensive validation the Invasive Sensing Mechanism (ISM) using more (ten) impact amplitudes and multiple bone models; Phase 2 (months 7-18) focuses on the development of the AI-PID instrument and its validation in acetabular models. Project milestones, scientific and statistical methods, expected outcomes, and potential problems are clearly identified and adequately addressed. The proposed work is innovative, and the approach seems well suited to test the research hypothesis.

1. Significance:

Strengths

- Despite the prevalence and success of total hip replacement (THR, over 400,000 procedures performed in the US each year), recent failure rates range from 25% to 50%. Many of these failures can be related to difficulties in assessing optimal implant stability: implants must be seated deep enough to obtain sufficient primary stability and prevent aseptic loosening, while avoiding fracture of bone.
- Current methods for press fit fixation are primarily qualitative, are not standardized, and are subject to great variability, especially for the less-experienced surgeons who perform 80% of such procedures.

- Moreover, an optimal endpoint for press fit fixation has not been clearly defined.
- There is clearly a need for advanced surgical technologies that can quantitatively accomplish the optimal press fit value for implant/bone interface, regardless of the variability, and provide a quantitative surgical endpoint for these THR.
- The proposed Invasive Sensing Mechanism (ISM) and Automatic Intelligent Prosthesis Installation Device (AI-PID) have the potential to address these needs by providing the appropriate number of impacts at the appropriate force amplitude. If successful, this technology could significantly impact surgical practice and improve patient outcomes.

Weaknesses

- None.

2. Investigator(s):

Strengths

- PI (Dr. Behzadi) is an orthopedic surgeon and president of Behzadi Medical Device (Pleasanton CA). He has a strong record of research and development, with several patents, in the field of orthopedics and fracture fixation.
- Co-Investigators (Dr. Bechtold, Dr. Mantell) are Professors at the University of Minnesota. Both have impressive records of research and publication related to experimental and computational biomechanics.
- Mr. Rusk is Director of Medical Devices at Boston Engineering. He has an impressive record of research and project management involving medical devices, and will oversee development of the AI-PID.
- Mr. Peterson will serve as Engineering Program Manager, coordinating efforts between the Excelen Bone and Joint team, the Mechanical Engineering team, and the Earl E Bakken Medical Devices Center.

Weaknesses

- Not a strong record of research collaboration between technical and clinical co-investigators directly related to the proposed research.

3. Innovation:

Strengths

- The proposed development and validation of technology that can help surgeons reliably apply the correct amount of force during THR, based on real-time measurements, is very novel and has the potential to significantly impact surgical procedure and patient outcomes.

Weaknesses

- None.

4. Approach:

Strengths

- The project involves an 18-month Fast-Track STTR plan of R&D: Phase 1 (months 1-6) builds on impressive prior work and focuses on more extensive validation the Invasive Sensing Mechanism (ISM) using more (ten) impact amplitudes and multiple bone models; Phase 2

(months 7-18) focuses on the development of the AI-PID instrument and its validation in acetabular models.

- Investigators have conducted preliminary studies using an oversized acetabular prosthesis, which was inserted into an undersized bone substitute cavity using a variety of impact forces (774-7,757 N). They hypothesize that the observed plateauing bone force, combined with observed relationships between insertion rate and extraction force, could be a quantitative measure of the quality of fixation.
- Project milestones, scientific and statistical methods, expected outcomes, and potential problems are clearly identified and adequately addressed. The proposed approach seems well suited to test the research hypothesis.

Weaknesses

- It is not clear how internal bone forces (F5) will be measured “with appropriately placed sensors”. Measuring internal forces in-vivo is much more challenging than measuring forces in sawbone models… what types of sensors will be used and how will they be implanted and calibrated?
- The stress-strain characteristics of human bone are nonlinear and strongly dependent on age, gender, porosity, etc… simple Hooke’s law models may not be inaccurate and may be difficult to calibrate.

5. Environment:

Strengths

- The R&D facilities at Earl E. Bakken Medical Devices Center and the Excelen Center for Bone & Joint Research and Education (University of Minnesota), combined with the technology development resources at Boston Engineering are well suited to the proposed research.

Weaknesses

- None.

Phase II (Type 2 R42 and Type 2 R44 applications):

Not Applicable

Direct Phase II (Type 1 R44 applications-See Face Page):

Not Applicable

Fast Track (Type 1 R42 and Type 1 R44 applications):

Not Applicable

Protections for Human Subjects

Not Applicable (No Human Subjects)

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender:

- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion of Children under 18:

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

CRITIQUE 2

Significance: 2
Investigator(s): 2
Innovation: 4
Approach: 5
Environment: 2

Overall Impact: This is a fast track STTR application to develop an automatic press fit fixation mechanism (AI-PID) for Total Hip Replacement (THR) procedures. If successfully developed, the proposed AI-PID can automatically assess the stress response of bone at the implant/bone interface and determine the “sweat spot” of pressing force value range that provides the “best fixation short of fracture (BFSF). The clinical benefits of this proposed device would be the standardization of application force to provide safe fixation while avoiding bone fracture, and quality assessment of the THR procedures.

The strengths of this application include: 1) Identification of a significant clinical problem in THR procedures; 2) PI is an experienced orthopedic surgeon; 3) Supporting team appears to be strong with expertise relevant to the project.

The weaknesses of this application include: 1) Rigor of the proposed technique: The proposed invasive sensing mechanism (ISM) appear to be pure empirical and does not seem able to provide in vivo measurement or feedback information to surgeons performing the THR procedures. The rationale and

the empirical model (e.g., Fig 1) appear to be overly simplified. For example, the degree pf implant fixation is mainly determined by the friction force between bone and implant surface, which is a result of interaction between the deformations on bone and implant. The proposed model does not seem to be able to address these contributing factors.

Overall this is an interesting proposal with clear clinical benefits. The rigor and clarity of theory and experimental design could be further improved.

1. Significance:

Strengths

- Identification of a significant clinical problem in THR procedures

Weaknesses

- The technique described in the proposal does not seem able to provide in vivo measurement or feedback information to surgeons performing the THR procedures. This may limit its applications.

2. Investigator(s):

Strengths

- PI is an experienced orthopedic surgeon;
- Supporting team appears to be strong with expertise relevant to the project.

Weaknesses

- None

3. Innovation:

Strengths

- The proposal attacks an important yet very challenging problem.
- Technique to achieve best fixation short of fracture (BFSF)

Weaknesses

- The proposed model seems pure empirical that may not be able to sufficiently take into consideration of many factors that affect the BFSF.

4. Approach:

Strengths

- Proposed a set of empirical models of estimate BFBF.

Weaknesses

- Rigor of the proposed technique: The proposed invasive sensing mechanism (ISM) appear to be pure empirical and does not seem able to provide in vivo measurement or feedback information to surgeons performing the THR procedures.
- The rationale and the empirical model (e.g., Fig 1) appear to be overly simplified. For example, the degree pf implant fixation is mainly determined by the friction force between bone and implant surface, which is a result of interaction between the deformations on bone and implant. The proposed model does not seem to be able to address these contributing factors.

5. Environment:

Strengths

- Appropriate.

Weaknesses

- None.

Protections for Human Subjects

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Inclusion of Women, Minorities and Children:

- Sex/Gender:
- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion of Children under 18:

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

CRITIQUE 3

Significance: 3
Investigator(s): 3
Innovation: 3
Approach: 4
Environment: 2

Overall Impact: This proposal attempts to develop a method of measuring forces to optimize implantation of the acetabular socket during hip replacement surgery. While the idea of quantifying the forces used to impress the acetabular socket into its final position is a potentially valuable method for reducing loosening of the acetabular socket, it is not clear that the proposed device can be fabricated and make the necessary measurements. A great deal of preliminary data based on phantoms and preliminary bone experiments support the idea of making these measurements. However, it is not clear that these measurements alone can improve outcomes when measured at the time of implantation. The proposed pressure sensors are a reasonable approach to address this problem. The instrumentation of the Automatic Intelligent Prosthesis Installation Device (AIPID) is novel, but it is not clear what level of pressures and sensitivity are required to obtain useful data. Given the heterogeneous nature of bone, this is particularly important. The Approach Section clearly outlines a well thought out series of testing algorithms. Overall, the proposed studies should yield valuable information, but it is not clear that this will be sufficient to cover the wide range of bone anomalies seen every day by the surgeon. Overall, this proposal has significant potential to bring a very useful orthopedic tool to the marketplace, if the PI and the team can resolve the issues regarding differences between in-vitro and in-vivo use.

1. Significance:

Strengths

- This proposal develops sensor technology to improve the socket fit in total hip replacements. Specifically, one of the major causes of morbidity from implanted hips is loosening of the socket which can be due to loosening of the acetabular prosthesis. This can result from many causes including fracture, bone loss, socket displacement, and infection. This proposal attempts to develop a device to optimize implantation of the socket at the time of initial implant. It achieves this goal by measuring bone compressibility parameters and the uniformity of the bone at the site of implantation. A series of mathematical models relate the values found during compression tests to numerical values that can be used to assess the suitability of a particular acetabular location for the location of the implant. If this project is successful, it would be a significant advance in total hip replacement surgery.

Weaknesses

- While the overall concept has value, it is not clear how much variability occurs in a millimeter-to-millimeter elasticity and compressibility. Bone is known to be highly heterogeneous in its properties, and it is not clear how many measurements will be required to achieve statistical significance. This uncertainty may complicate the proposed study. Similarly, bone from various ages and sexes will have different properties.

2. Investigator(s):

Strengths

- The PI Kambiz Behzadi M.D., is President of Behzadi Medical Device LLC, and also has a Private Orthopedic Surgery Practice, in Pleasanton, CA
- Consultant: Joan Bechtold Ph.D., is Professor & Director of Orthopedics Biomechanics Laboratory, Univ. of Minnesota in Minneapolis, MN. She is the Gustilo Professor of Orthopedic Research, Dept. of Orthopedic Surgery and Hennepin County Medical Center (MMRF), University of Minnesota. She is also Vice-Chair Research, Dept. of Orthopedic Surgery University of Minnesota, Minneapolis, MN
- Technical Project Lead: Susan Mantell Ph.D., Morse Alumni Distinguished Professor of Mechanical Engineering, Univ. of Minnesota.
- Engineering Program Mgr.: Gregory Peterson MBA, Director of Innovation Collaborations, UMN Bakken Medical Devices Center, Univ. of Minnesota
- Contract Project Mgr.: Jesse Rusk MBA, Director of Medical Devices, Boston Engineering LLC, in Waltham, Massachusetts
- This is a strong engineering team combined with the excellent orthopedic knowledge of the clinicians.

Weaknesses

- The team might benefit from the addition of a bone pathologist.

3. Innovation:

Strengths

- Overall this is an innovative use of sensor technology to evaluate the forces at work during the placement of acetabular hip implants. The overall concept of a multi-sensor device to serve as

a guide to treatment is valuable. In addition, the development of special sensors for specific conditions should provide the desired information.

Weaknesses

- It is not clear how sensors on multiple axes will integrate information down to just one number, and how this number becomes representative of the likelihood of successful implantation. Clearly, having improved quantification of implant forces could generate stronger implants with fewer acetabular loosening over time. Such a determination will require long-term in-vivo human studies for validation.

4. Approach:

Strengths

- Preliminary work is clearly detailed in the Preliminary Reports Section. Similarly, a series of in-vitro stimulate is proposed to initially test and calibrate devices for sensing learners' performance using the Automatic Intelligent Prosthesis Installation Device (AIPID). A second system is dedicated to learners working with well-known orthopedic equipment to compare performance values. Finally, a 2nd series of in-vitro phantom studies is proposed using the fabricated device.
- The proposal describes the fabrication of an entirely new sensor array at the end of the program to shrink its size and make it more robust to noise and more practical for use by surgeons.
- Despite the lack of specifics, the overall concept has substantial merit, particularly if the device can quantify the pressures and forces occurring in the acetabular implantation.

Weaknesses

- The proposal contains substantial speculation as to the ability of the group to fabricate the actual proposed device. Unfortunately, no clear metrics for device performance are provided, and it is not clear what will be the specific endpoints for choosing sensors in the proposed Automatic Intelligent Prosthesis Installation Device (AIPID). The adaptation of the device for use in a small-scale feasibility trial using a large animal model would provide substantial confidence that the device functions as designed in the clinical setting.
- Timelines for Phase I and Phase II are presented, but it is unclear what metrics will be used to assess the success or failure of each phase.

5. Environment:

Strengths

- Excellent.

Weaknesses

- None.

Fast Track (Type 1 R42 and Type 1 R44 applications):

Acceptable

Protections for Human Subjects

Not Applicable (No Human Subjects)

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Inclusion of Women, Minorities and Children:

- Sex/Gender:
- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion of Children under 18:

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

- NOTE: DISCUSS AT STUDY SECTION....

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R42 AR074853-01; PI Name: Behzadi, Kambiz

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
Cardiovascular and Surgical Devices
ZRG1 SBIB-Y (12)
06/14/2018

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

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constitute or appear to constitute a conflict of interest.