ABSTRACT OF RESEARCH PLAN

PROJECT TITLE:

An imaging framework for clinically testing new treatments to prevent post-traumatic OA

Abstract of research plan: Please provide an abstract of 250 words or less with 5 underlined phrases for a project summary. Please avoid summaries of past accomplishments and the use of the first person. The abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application.

Research is desperately needed to improve the management of intra-articular fractures and to enable the prevention of post-traumatic osteoarthritis. It is virtually impossible today for a treating physician to reliably predict who will develop arthritis after an intra-articular fracture, over what timeframe, or how disabled it will leave them.

The immediate goal of the proposed research is to test the value of a new low-cost, low-dose standing CT system for efficient early detection of both joint degeneration and elevated contact stress. The standing CT scanner holds promise for detecting arthritic changes earlier than other imaging modalities because of the combination of its 3D nature and ability to image joints in a weight-bearing pose. A secondary goal of the proposed research is to enable predictive models for osteoarthritis risk based on measures of post treatment contact stress, both to inform treatment and so that new interventions can be tested in a manner incorporating risk stratification. We propose a prospective multi-center clinical study of patients having sustained intra-articular fractures of the tibial pilon. Radiographs and CT scans obtained at follow-up clinical visits will be collected and used to evaluate joint degeneration. Clinical outcome data will also be collected. Aim 1 is to determine the extent to which osteoarthritis findings on standing CT correlate earlier and more strongly with joint symptoms than findings on plain radiographs. Aim 2 will establish the relationship between contact stress computed from baseline standing CT scans and longitudinal changes in the 3D joint space width.

SECTION 3

FACILITIES – Laboratory Space and Major Equipment

Please provide an accurate description of laboratory facilities and major equipment available at the grantee's institution that will support this project. Please recall the list of supplies and support that the grantee's institution, or grant funds other than those from the OTA, are expected to provide:
click to see the list

Laboratory Space: The University of Iowa

The Orthopaedic Biomechanics Laboratory occupies 22 individual rooms (5,333 sq ft) in contiguous space on the ground floor of the Westlawn Building at the campus of the University of Iowa. The Laboratory is configured primarily for macroscopic-level physical testing of musculoskeletal constructs (e.g., bones, articular joints, orthopaedic implants) and for corresponding computational modeling. The physical testing area includes a 320 sq ft multi-purpose wet lab, a 360 sq ft multi-purpose dry lab, a 320 sq ft surgical preparation room, a 750 sq ft mechanical testing room, a 360 sq ft machine shop, and a 250 sq ft specimen storage area. The computational modeling area (380 sq ft) is has 8 separate workstation seats in two adjoining partially partitioned areas. Adjacent to these core operational areas are 3 faculty offices, 7 research staff offices, 3 student/fellow offices (4 desk spaces each), an administrative/reception area (330 sq ft), and a library and conference room (450 sq ft).

Directly relevant to the proposed research, the laboratory has an extensive platform for computational modeling and analysis. An HP Proliant DL380 server with 2 Dual-Core 2 GHz Intel Xeon processors provides primary lab access to an HP Integrity rx4640 with 600 GB fibre channel hard disk drive, an HP xw8400 with 2 Dual-Core 3 GHz Intel Xeon processors, and an HP xw8400 with 2 Quad-Core 3 GHz Intel Xeon processors. The Proliant server runs RedHat server OS for its 1TB internal and 12TB external disk arrays. The Integrity system uses a 64-bit HP-UX operating system, while the xw8400 workstations run under open SUSE. All three are specially tailored to perform very large nonlinear, large deformation, finite element analysis contact problems, as well as computational fluid dynamics and fluid-structure interaction problems (ABAQUS, ADINA). Three-dimensional finite element model generation (PATRAN, TrueGrid) can begin with manufacturer's blueprints or with engineering drawings (Creo, AutoCAD, VectorWorks). Alternatively, models are generated directly from medical images (CT, MRI, and plane-film) using OsiriX, Geomagic Studio/DesignX, and/or MATLAB on desktop personal computers. Medical image segmentation is facilitated by two Wacom Cintiq 21UX interactive pen displays. Finally, a NextEngine Desktop 3D scanner affords laser surface scanning capability, when geometry must be derived from physical objects.

Desktop PCs are maintained in each of the faculty, staff, and student/fellow offices. NoMachine's NX server, SAMBA, and Secure-Shell permit direct access to both laboratory and remote computers from the desktop PCs. Networked PC's operate the MTS Insight, MTS Bionix and MTS 810 materials testing machines, the Flock of Birds motion tracking system, LabView data collection through a National Instruments SCXI A/D converter, an RDI 8/12-bit whole-film transmissive scanner, and a Microtek ScanMaker 9800XL large format flatbed scanner with TMA 1600 transparency media adapter. Printing is provided by HP 4100TN duplex B/W and HP 4650DN duplex color laser printers. Laboratory personnel also maintain seven laptops: two for database compilation at Des Moines Orthopaedic Surgeons PC for ongoing collaborative studies of total hip and knee follow-up, and five for off-site data collection and ad hoc travel use.

Equipment:

Digital radiography systems and pedCAT SCT scanners are available at all three clinical sites.

Clinical Facilities: The University of Iowa

The clinical programs at the University of Iowa Department of Orthopedics and Rehabilitation occupy 70,000 sq ft in a modern facility completed in 1995. The Department of Orthopaedic Surgery includes faculty offices, multiple teaching facilities including seminar rooms and an auditorium, outpatient clinics, and a physical therapy unit including specialized programs in arthritis, sports medicine, hand care and spine care. The orthopaedic faculty includes 30 full-time assistant, associate or full time professors of orthopaedic surgery who practice orthopaedics and conduct clinical and basic research. The clinical faculty provide care for patients with all types of musculoskeletal injuries and diseases, and have established specialized clinical services that include arthritis and joint reconstructive surgery, sports medicine, adult back disorders, microvascular surgery, musculoskeletal oncology, hand and upper extremity surgery, musculoskeletal trauma, and pediatric orthopaedics. The faculty log about 73,000 outpatient clinic visits/year and are responsible for performing about 7,000 surgical procedures per year. In addition, the faculty provide the orthopaedic service at the Iowa City Veterans Administration Medical Center. This service has a total of 2,000 outpatients per year and about 400 surgical procedures. All computer resources required for the study have been provided and are already in place.

Clinical Facilities: The University of Utah

The University of Utah Health Sciences Center is a regional Level One academic trauma Center covering orthopaedic trauma surgery for a catchment that includes approximately 10% of the lower 48 states. The University Orthopaedic Center (UOC) is a 100,000 sq ft facility that houses many orthopaedic sections from sports medicine to trauma surgery to physical therapy. The Orthopaedic Center has five operating rooms, six overnight patient suites, PACU, six post-operative rooms, MRI, 45 clinical exam rooms, three diagnostic radiology suites, a physical therapy and pool area, and a full-service pharmacy. In addition to the clinical facilities, the UOC features a library, faculty offices, three conference rooms, a wet lab, a dry lab, biomedical testing facilities, and cadaveric study laboratory. With greater than 10,000 clinic visits per year, the University Orthopaedic Center the optimal place to conduct clinical research on patient outcomes. The facility has a full staff of medical assistants, nurses, physicians' assistants, patient administrative staff, and research administrative staff to facilitate clinical investigations, and clinic staff are trained and accustomed to the regular administration of PROMIS measures for patients. All computer resources required for the study have been provided and are already in place.

Clinical Facilities: The University of Washington

Based at Harborview, UW Medical Center, Northwest Hospital, and the Eastside, the Department of Orthopaedics and Sports Medicine provides comprehensive services in the areas of Arthritis, Foot and Ankle, Fractures and Trauma, Hand and Upper Extremity, Hip and Knee, Metabolic Bone Disease, Oncology, Pediatrics, Shoulder and Elbow, Spine, and Sports Medicine. The UW Orthopaedics program ranked among the top programs in the U.S., according to U.S. News & World Report 2014-2015 rankings. UW Orthopaedic clinics provide comprehensive care, consultation and surgery to some of the most complex orthopaedic injuries throughout the region. Colleagues in rehabilitation medicine, neurology, rheumatology and other fields of care ensure that the most appropriate, considered care for each patient's problem is provided. The goal is to return people to normal life activities, at work and at play – whether that involves riding a bike, pouring tea or throwing a ball. We want to help our patients recapture their quality of life. All computer resources required for the study have been provided and are already in place.

SECTION 4

RESEARCH PLAN

A. SCIENTIFIC AIMS

Surgeons treat high-energy intra-articular fractures (IAFs) by reducing and stabilizing the joint, but disabling post-traumatic osteoarthritis (PTOA) nonetheless all-too-often ensues. Recent research indicates that IAFs initiate a sequence of biologic events triggering joint degeneration. Strong evidence is emerging that new biologic agents could mitigate or arrest these events.

These findings offer hope for a paradigm shift in treating IAFs, but controlled clinical trials are needed. Two major barriers remain: (1) it takes years to determine if new treatments work because PTOA develops relatively slowly and early changes are difficult to detect and (2) it is difficult to predict PTOA risk, making it virtually impossible to do controlled clinical trials.

As for detecting PTOA early, IAF patients are followed with radiographs, which are insensitive to detecting OA until later stages. A new upright standing CT (SCT – Figure 1) scanner has promise to detect OA earlier, because of its 3D nature and ability to image in a weight-bearing pose. This advance comes at a cost similar to plain radiographs and an equivalent Relative Radiation Level. The small footprint of the scanner and lack of ongoing fixed costs permits even small community clinics to offer SCT. SCT-enabled imaging biomarkers could advance clinical care and hasten the pace of discovery.

Figure 1. The standing CT (SCT) system, pedCAT, is an in-office scanner for advanced imaging of the foot and ankle.

Regarding PTOA risk prediction, we have developed CT-based methods to quantify IAF severity and elevated contact stress from residual incongruity, influential mechanical risk factors. In a prospective study of tibial pilon fractures, patients stratified using these metrics showed thresholds above which PTOA was nearly inevitable. This presents an objective means to risk-stratify patients for controlled clinical study.

The objective of the proposed research is to establish a more sensitive SCT-enabled imaging biomarker for PTOA. Coupling this biomarker with methods for assessing mechanical risk factors using images from the SCT will enable better prediction, earlier diagnosis, and more meaningful longitudinal assessment of PTOA. This will lead to better-informed treatment decisions and provide a framework for the clinical testing of new biologic treatments to prevent or forestall PTOA.

The aims of the proposed research are:

Aim 1 Determine the extent to which OA findings on SCT correlate earlier and more strongly with joint symptoms than findings on plain radiographs.

Aim 2 Measure the incidence of PTOA following surgical fracture reduction in patients with tibial pilon fractures and quantify the extent to which post-reduction contact stress predicts risk and correlates with changes in 3D joint space width.

B. BACKGROUND & SIGNIFICANCE

Post-traumatic osteoarthritis (PTOA) is a common disabling condition following IAFs, despite best treatment efforts.[1,2] Between 23% and 44% of patients develop PTOA after tibial plateau fractures[3-5] and >50% of patients after tibial pilon fractures.[6-11] In one study, 30% of ankles had PTOA within 2-4 years after a pilon fracture.[11] PTOA brings substantial pain, disability, lost work capacity, and decreased general health status. In the ankle, where the vast majority of OA is post-traumatic, the associated impairment is comparable to that caused by end-stage kidney disease or congestive heart failure.[12,13] The societal cost of PTOA is high (~$12 billion/year in the U.S.),[13] since pain and lost function frequently leads to lost work capacity.

Recent findings indicate that IAFs, by virtue of both acute and chronic mechanical factors, initiate a sequence of biologic events leading to PTOA.[14] Clinical trials of agents aimed at interrupting this sequence of events face barriers of limited capability to predict PTOA risk and poor early indicators of PTOA development. We have established methods to quantify PTOA risk from mechanical factors, a critical step in overcoming these barriers.

There remains an urgent need for better PTOA imaging biomarkers. Diagnosis and prognosis, as well as evaluation of therapeutic efficacy, require biomarkers sufficiently sensitive to detect development and progression of disease.[15]

Clinical monitoring for PTOA following IAF presently involves the serial acquisition of weight-bearing radiographs to check for joint degeneration.[16] However, radiographs capture an obscured 2D projection of a complex 3D structure and pathology. Our working hypothesis is that a low-dose standing CT (SCT) scanner for the foot and ankle will provide more sensitive and responsive measures of joint degeneration, without an increase in cost or time and without a significant increase in radiation.[17] SCT would provide much greater diagnostic value, not only because of its 3D nature, but also because patients are imaged in a functional weight-bearing position. The SCT scanner will also simplify articular contact stress computation and could guide earlier preventive therapies.

Achieving the aims of the proposed research will significantly enhance the assessment and treatment of IAFs, thereby promoting excellence in care for the injured patient (OTA Mission). Imaging biomarkers from Aim 1 will detect joint damage earlier, advancing clinical care and the pace of discovery. A better understanding of how altered contact stress leads to PTOA (Aim 2) will open the way toward integrating better prognostic ability into the treatment of patients with IAFs.

C. PREVIOUS WORK DONE ON THE PROJECT

Over the past fifteen years, our group pioneered tools for the objective assessment of mechanical factors involved in PTOA development following IAF (Figures 2 and 3),[18-26] work awarded the 2011 OREF Clinical Research Award. In a prospective single-center study of tibial pilon fractures, patients stratified using the quantitative metrics demonstrated a threshold for fracture severity and contact stress exposure, above which PTOA was nearly inevitable.[20,26] Patients whose joints had contact stress exposure exceeding a critical threshold developed PTOA within two years after injury. Using contrast-enhanced CT, we established that cartilage loss over time was greatest at sites with the highest exposures (Figure 4).[27] This required careful alignment of bone segmentations obtained at different follow-up times, similar to what will be required in the proposed research.

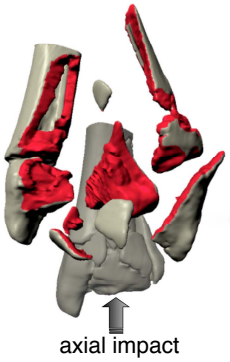

Figure 2. Custom-written software is used to measure the area of inter-fragmentary bone surfaces. The fracture-liberated surface area and the bone densities across that surface are used to calculate fracture energy. The length of the edge between the subchondral and interfragmentary bone surfaces (the articular fracture edge length) is used to quantify articular surface involvement.

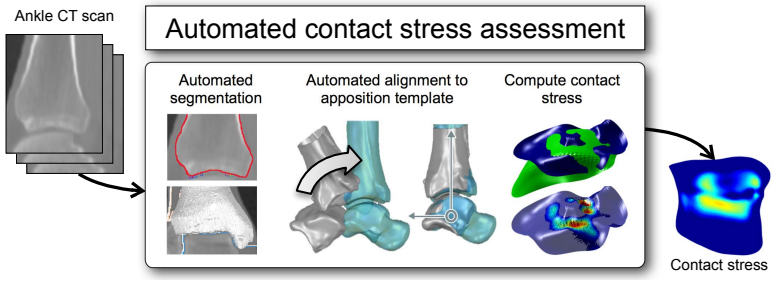

Figure 3. This schematic depicts automated methods for contact stress assessment working from post-op CT scans.

In follow-on work exploring the hypothesis that fracture severity metrics are higher in pilon than in plateau fractures, fracture severity is being studied in a larger and more diverse group of patients.[28,29] Seventy-five tibial plateau fractures and fifty-two tibial pilon fractures from our multi-institutional study group were selected to span the spectrum of severity. The ranges of fracture energies measured for tibial plateau and pilon fractures were 3.2 to 33.2 Joules (J) and 3.6 to 32.2 J, respectively, and articular fracture edge lengths were 68.0 to 493.0 mm and 56.1 to 288.6 mm, respectively. There were no differences in the fracture energies between the two fracture types, but plateau fractures had greater articular fracture edge lengths ($p<0.001$). Interestingly, AO/OTA fracture classifications generally reflected severity, but there was substantial overlap of severity measures between different classes. This finding highlights limitations in relying on fracture classification as a surrogate for severity.

Our work demonstrating the basic clinical utility of SCT in imaging OA features has been in the knee, using a prototype system based on the pedCAT scanner. We have shown that the sensitivity, accuracy and negative predictive value for detecting osteophytes is substantially higher

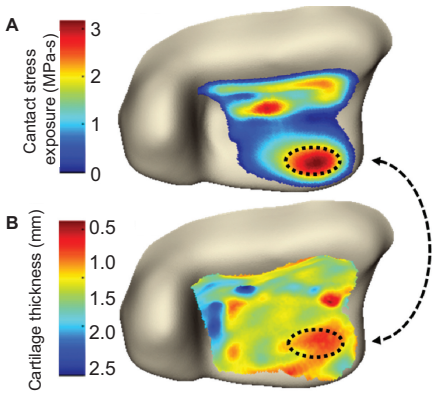

Figure 4. A) These plots depict (A) the contact stress exposure computed from post-op CT and (B) the cartilage thickness measured from contrast-enhanced CT at 18 months post-op over the joint surface. The cartilage showed thinning in areas of substantially elevated contact stress.

with SCT imaging than radiographs.[30] The 3D joint space width (JSW) is then defined as the distances between the nearest points on two bone surfaces (Figure 5). The percent of the apposed joint surface area with a JSW below a nominal proximity threshold was used as a summary 3D JSW measure. The percent of the joint surface area with 3D JSW<2.5mm obtained using SCT correlated much more highly with articular cartilage morphology evaluated on MRI[31] than did radiographic JSW (r=0.84 vs. 0.66).[32]

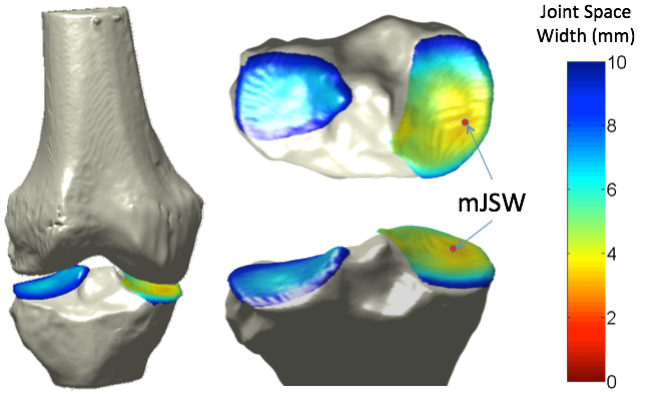

Figure 5. Tibia and femur bones were segmented from the SCT to produce 3D models. The proximity of the bones is reported as a JSW map.

D. METHOD

We propose a prospective clinical study of patients having sustained IAFs of the tibial pilon. De-identified imaging studies will be sent to Iowa, where JSW metrics will be computed and other joint degenerative assessments made. Clinical outcome data will be collected and sent to Iowa for analysis. Finally, we will examine the relationship between contact stress computed working from the baseline SCT scans (obtained after fractures of the tibial pilon have healed) and changes in the 3D JSW.

Sample Characteristics: We will enroll patients with IAFs of the tibial pilon. Dependent variables will be patient-reported clinical outcomes and PTOA status based on radiographs obtained at final follow-up. The independent variable will be SCT assessments of joint degeneration, 3D JSW and contact stress exposure. The target sample size is 50 patients. An audit of recent case volumes across the clinical sites showed that 253 pilon fracture cases were treated in a recent year. Assuming 50% enroll, we will reach target enrollment within 6 months.

Patients from skeletal maturity to age 70 with unilateral fractures of the tibial pilon (classified as B-2, B-3, C-1, C-2, or C-3), identified within four weeks of injury, will be included. Exclusion criteria are bilateral fractures, ipsilateral calcaneus or talus fractures, type III open wounds,[33] and patients with an Injury Severity Score of 18 or greater.[34] Fractures secondary to neuropathy and severe osteopenia will be excluded. Fractures with previous attempts to surgically reduce the joint, and those that initially present greater than 4 weeks after the initial injury, will be excluded. Pregnancy, previous fracture involving the same joint, and intervening joint trauma between the index injury and the final follow-ups are additional exclusion criteria.

Treatment Course: All fractures will be managed with standard-of-care techniques chosen by the treating surgeon. Post-op care will include non-weight-bearing for 6-12 weeks after the injury. Patients will be followed according to standard-of-care and complications requiring treatment recorded. Patients developing non-unions or deep infections (previously about 5% of patients) will be excluded from analysis. Critical follow-up for outcomes will be at 6, 12, and 18 months after injury.

Radiographs: Radiographs of the injured joint will be obtained at presentation and after surgical interventions. Post-op radiographs are obtained in standard views (AP, lateral and mortis). Additional weight-bearing radiographs will be obtained at 6, 12, and 18 months after injury.

CT scans: CT scans standardly obtained upon presentation will be used to measure fracture severity.

Severity assessment: Fracture severity will be measured in all patients using objective metrics.[19,26,35] Briefly, the bone inter-fragmentary surface area will be measured from CTs using established computational methods (Figure 2). Bone density from CT enables calculation of fracture energy. Additionally, the length of the fracture edge involving the articular surface provides another key measure reflecting severity.

SCT scans: SCT scans will be obtained at three points in time. The first scans will be acquired six months after injury; the fracture will be healed but may not yet have been subjected to significant contact stress from loading, and any external fixators used for treatment will have been removed. Additional SCT scans will be obtained at 12 and 18 months after treatment.

SCT 3D JSW: A 3D dataset with isotropic resolution of 0.37mm will be reconstructed. Assessment involves segmentation of digital surface models of the apposed bones from the SCT images. The 3D JSW is then defined by the distances between nearest-neighbor points on the two surfaces, mapped over the entire surface.

Clinical outcome assessment: The validated Ankle Osteoarthritis Scale (AOS) will be obtained for all patients. It provides an overall assessment of ankle status as well as a specific assessment of pain and disability.[36,37]

Final PTOA assessment: Weight-bearing radiographs and SCT of the joints examined at 18 month after injury will be used to characterize the development of OA.[38] Three observers will do all assessments in a single sitting. Ratings will be done separately to assess agreement, and discrepancies will be resolved by consensus.

Aim 1: Determine the extent to which OA findings on SCT correlate earlier and more strongly with joint symptoms than findings on plain radiographs.

We will assess both concurrent validity of OA features on SCT and radiographs with pain severity and physical function, as well as predictive validity for worsening at 18-month follow-up. Radiographic severity of OA is not associated with either pain[39,40] or physical function.[41-43] Evidence of stronger relationships between SCT imaging findings and pain and physical function would advance ability to predict symptoms and function.

Assessment of pain and physical function: This study will utilize the AOS ankle pain (primary) and physical function subscales to assess worsening of joint pain. Patients undergoing ankle fusion or arthroplasty by final follow-up will be deemed to have had worsening of joint pain/function.

Sample Size: Based on published associations between radiographic OA, pain, and function,[40,44] a total of 45 subjects would provide 86% power for the one-sided McNemar test to detect the difference between the sensitivity values of 7% vs. 52% for the two imaging approaches at alpha=0.025 level (Bonferroni correction for the cross-sectional and longitudinal assessments). Recruiting 50 subjects will retain sufficient statistical power to achieve our Aims, while accounting for up to 10% rate of missing outcome data.

Statistical analysis: Associations between continuous baseline AOS pain and function scores and ordinal a) osteophyte and b) JSW on SCT and radiographs will be assessed by calculating Spearman correlation coefficients. We will then test for the equality of dependent correlations from radiographs and SCT.[45]

Aim 2: Measure the incidence of PTOA following surgical fracture reduction in patients with tibial pilon fractures and quantify the extent to which post-reduction contact stress predicts risk and correlates with changes in 3D joint space width.

Contact stress assessment: The habitual contact stress exposure will be assessed in patients using our existing computational methods (Figure 3).[25,46] We will utilize SCT scans obtained at the 6-month follow-up visit to obtain 3D bony geometries. The mechanical analysis then involves the application of loads representing appropriate percentages of the patient's body weight at a series of poses in gait. Contact stress distributions obtained at each of these poses are integrated into a contact stress-time exposure metric.

Data analysis/Sample Size: To evaluate whether contact stress independently predicts PTOA at 18 months, we will fit a logistic regression model with PTOA status as the dependent variable and injury severity and contact stress as independent variables. We will test null whether the coefficient for contact stress differs from zero at the 0.05 type-I error level. For power calculation, we made the following assumptions: (1) the correlation between fracture severity and contact stress is 0.5 and (2) the incidence of PTOA by 18 months at the mean value of contact stress is 20%.[47]

Potential problems and alternative approaches

A primary concern in any clinical study is that we might be unable to gather sufficient numbers and quality of imaging and follow-up/outcomes information. However, since the clinical volume for our team exceeded 250 patients in 2015, we are confident that we will be able to identify and analyze the 50 patients (<50% of the potential pool) as proposed. In the event that there are incomplete data sets, we will perform separate statistical analyses to accommodate whatever data are missing.

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BUDGET

SALARIES AND WAGES (List all personnel for whom money is requested)	% effort on project	Requested from OTA (round to $)
Graduate Research Assistant	25 %	$ $ 13,449
	%	
	%	
	%	
Fringe Benefits ___20.32_% of Salaries and Wages Salaries and Wages plus Fringe Benefits	TOTAL	$ 16,182

PERMANENT EQUIPMENT (append justification)	
Subtotal	$ 0

CONSUMABLE SUPPLIES (exclude animals and animal care)	
Subtotal	$ 0

ANIMALS AND ANIMAL CARE	
Subtotal	$ 0

ALL OTHER EXPENSES	
Iowa subject compensation	$ 1,400
Iowa subject imaging	$ 6,900
Subawards to Utah and Washington	$ 54,000
travel to present research at OTA Annual Meeting	$ 1,500
Subtotal	$ 63,800

TOTAL DIRECT COSTS $ 79,982