

--- Today's Date ---

06/28/2023

--- Name of 501(c)(3) Organization ---

University of Pennsylvania School of Veterinary Medicine

--- Federal Tax-Exempt ID# ---

23-1352685

--- Year Established ---

1740

--- Amount Requested ---

\$20,000.00

--- Name of Executive Director ---

Elizabeth Peloso

--- Mailing Address ---

3541 Walnut St., Franklin Bldg. 5th Floor Philadelphia, PA
19104

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pennaors@lists.upenn.edu

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+12158987293

--- Organization's website ---

<https://researchservices.upenn.edu/>

--- Link to Organization's most recent filed IRS Financial Statements (#990): ---

https://apps.irs.gov/pub/epostcard/cor/231352685_202106_990_2022071120200882.pdf

--- Upload Organization's most recent filed IRS Financial Statements (#990) ---

<https://www.terfusa.org/wp-content/uploads/wpforms/809-8fba8c278fa5e5fb5fb2cbe55842a214/Trustees-2020-Form-990-FY21-PD-5fefa85eae35380379005f1c746e5638-1.pdf>

--- Farm/Facility Name ---

New Bolton Center

--- Farm/Facility Physical Location (City, State, Zip) ---

Kennett Square, PA 19348

--- Farm/Facility Mailing Address ---

382 West Street Rd
Kennett Square, PA
19348

--- Contact Name and Title ---

Holly L. Stewart, Assistant Professor of Large Animal Surgery

--- Contact Work Phone ---

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--- 1. Brief mission statement and describe the distinguishing features of your organization that supports the mission of TERF and the relevance to this proposal. ---

The mission of the University of Pennsylvania's New Bolton Center is to improve the diagnosis, treatment, and prevention of clinical conditions reducing the performance and livelihood of performance horses. One branch of these efforts has been directed toward the use of new imaging modalities and techniques that contribute to a greater understanding of clinical conditions. New Bolton Center's large animal surgery team evaluates and surgically repairs nearly two dozen racehorses with condylar fractures of the third metacarpal/tarsal bones each year. We have identified a need within the racehorse industry to improve our clinical ability in providing a prognosis on these injuries at the time of surgery. Although the outcome of these fractures is likely multifactorial, the native tissues of the joint—namely the articular cartilage and underlying subchondral bone—likely play a central role in fracture healing, joint health, and therefore return to athletic use. The overall goal of this project is to assess the articular cartilage and subchondral bone of racehorses with naturally occurring condylar fractures using arthroscopy and computed tomography (CT) to understand the relationship between tissues of the joint and develop more objective metrics that may assist in predicting case outcome. New Bolton Center is uniquely positioned in its case population to clinically evaluate, treat, and facilitate short- and long-term case follow-up for racehorses with condylar fractures.

--- 2. Briefly outline 3-5 goals for the requested funds and how these goals support your mission. ---

The overarching objective of this study is to explore the relationship between different tissues in the joint and how the health of those tissues may relate to the clinical outcome of racehorses with condylar fractures. The specific aims toward this objective are as follows:

- a. To correlate the arthroscopic appearance of the articular cartilage and computed tomographic density patterns of subchondral bone in racehorses with naturally occurring condylar fractures. We hypothesize that extensive remodeling or sclerosis of the subchondral bone will be associated with more damage to the articular cartilage.
- b. To compare the arthroscopic appearance of the articular cartilage and computed tomographic density patterns of the subchondral bone with the short- and long-term clinical outcome of racehorses with condylar fractures. We hypothesize that racehorses with more articular cartilage damage and/or increased subchondral bone density will require a longer post-operative convalescence and may be less likely to return to athletic use.
- c. Secondly, this project is intended to develop more objective metrics for creating an accurate prognosis for condylar fractures in racehorses. Misinformation about orthopedic injuries in racehorses has substantial social and economic effects on the racing community, and greater efforts are needed to provide objective data for reference. Outcomes from this project will be disseminated to the veterinary community through manuscript publication and presentation at local and national veterinary meetings. Outcomes of this project will be communicated to the general equine community informally through conversations with clients, owners, and trainers, and formally through community seminars and events, which are already in place as a part of the outreach programs at New Bolton Center.

--- 3. Provide a detailed description of the proposed project, how it is related to the mission of TERF and how it will impact the health and welfare of the horse. (Note: research applications should be understandable to a non-scientific audience and include sufficient detail and rigor for the scientific reviewers.) ---

Background – Historically, the investigation of joint disease has primarily been focused on the articular cartilage. The current paradigm for understanding joint disease focuses on the joint as a whole, organ (1), which means that all the tissues of the joint play an important role in joint health and function. The relationship between the articular cartilage and underlying subchondral bone has received a growing amount of attention, due to the physical proximity of these tissues within the joint. The interplay between the subchondral bone and articular cartilage is critical for maintaining joint health and early damage in one tissue has been shown to affect the functions of the other.(2,3)

Condylar fractures of the third metacarpal/tarsal bone (MC3/MT3) represent 15-26% of racehorse fractures that occur in the absence of trauma(4), and in conjunction with other fractures of the distal limb remain the most common cause of lost training days and euthanasia in the Thoroughbred racehorse.(5) Condylar fractures are believed to occur secondary to a failure in adaptive remodeling of the subchondral bone secondary to cyclic loading of the bone produced by training.(6) Numerous studies have investigated subchondral bone modeling in distal MC3/MT3 (7–10), but an antemortem investigation of the subchondral bone and articular cartilage has not been performed. There is a critical need to investigate how changes within the subchondral bone may be impacting the health of the

articular cartilage to better understand the impact condylar fractures have on long-term joint health and function.

Project overview – A prospective, multi-method comparison design will be used to compare the arthroscopic appearance of the articular cartilage and density patterns within the subchondral bone on computed tomography (CT) in horses with naturally occurring condylar fractures in MC3/MT3. Findings from this research will help strengthen the understanding of the relationship between articular cartilage and subchondral bone for joint health.

Case selection – Data will be collected on a total of 20 client-owner Thoroughbred racehorses with condylar fractures referred to New Bolton Center for evaluation and internal fixation. All fracture locations (i.e., forelimb vs. hindlimb), configurations (i.e., lateral vs. medial, complete vs. incomplete, unicortical vs. bicortical), and horse signalments (age, sex) will be eligible for inclusion. Thoroughbred horses not in active training or racing, those with additional fractures in other bones, cases that are deemed to be critical or hemodynamically unstable for the additional anesthesia time (see below) by a board-certified veterinary anesthesiologist, and those with fractures to be repaired under standing sedation will be excluded from the study. Condylar fractures of MC3/MT3 will be made based on radiography or CT of the affected limb. Prior to internal fixation, owners will be offered the opportunity to participate in the study. If the client agrees to participate, a CT examination (i.e., MC3/MT3 and associated metacarpo/tarsophalangeal (fetlock) joint) and arthroscopic evaluation of the fetlock of interest will be performed under the same anesthetic episode as internal fixation. This study design will add 20 minutes (maximum) to the anesthetic time. Costs associated with CT and arthroscopy will be covered through this proposed research.

Patient outcome – Patient outcome will be determined by telephone conversations with owners, trainers, or referring veterinarians, or on the basis of re-examinations performed at New Bolton Center. Data from Equibase may also be used, if necessary to determine long-term outcome.

Computed tomography (CT) – Images will be acquired with the horse under general anesthesia in lateral recumbency prior to internal fixation of the fracture. CT imaging will be performed using a commercially available 16-slice mobile CT scanner (OmniTom; NeuroLogica) acquired at an exposure of 120 kV and 20 mA in the transverse plane, with a slice thickness of 1.25 mm and volumetric resolution of 0.25 mm. Imaging studies will be stored in a standard DICOM format for analysis.

Metacarpo/tarsophalangeal (fetlock) joint arthroscopy – Arthroscopic evaluation of the fetlock joint associated with the affected MC3/MT3 will be performed under general anesthesia. Briefly, a 4.5 mm, 30-degree arthroscope will be inserted into the joint after distension with isotonic fluids. The lateral and medial articular cartilage on the dorsal and palmar/plantar aspects of MC3/MT3 will be evaluated. If visible, the condylar fracture and degree of fracture reduction will also be evaluated. Arthroscopic evaluation will be video recorded, and the lead surgeon will be asked to grade the appearance of the articular cartilage using a previously validated semi-objective 0-4 scoring system.⁽¹¹⁾ Briefly, a grade 0 indicates normal cartilage, grade 1 cartilage swelling and softening, grade 2 superficial fibrillation, grade 3 deep fibrillation down to subchondral bone, and grade 4 exposure of subchondral bone. Arthroscopic skin incisions will be closed routinely following arthroscopy.

Image evaluation – CT images will be analyzed in their original DICOM format to minimize data loss using similar methods as described by Posukonis et al.⁽¹⁰⁾ Briefly, CT images will be segmented by pixel values corresponding to Hounsfield units (HU) and density patterns of bone will be visually assessed using a 0-3

semi-objective grading scale to facilitate comparison between objective (computed) and subjective (observer) analysis. Grading of arthroscopic images will be used to provide a total cumulative joint score, and analysis will be further divided by regions within the joint (i.e., dorsal, palmar/plantar, proximal sesamoid bones).

Statistical analysis – Descriptive statistics will be reported for all enrolled cases, including age, breed, sex, and limb affected, as well as any other salient clinical information. All statistical analyses will be performed using commercially available software (R software in RStudio). Categorical data will be reported as median +/- interquartile range. Data normality will be assessed using Shapiro-Wilk testing and quantile-quantile plots. A linear mixed model with Tukey-Kramer pairwise comparisons (parametric) or Wilcoxon signed rank test with pairwise comparisons (non-parametric) will be used to compare findings between CT and arthroscopic images and between imaging findings and outcome. Fracture type, limb, horse age, breed, and sex will be evaluated as random effects and potential interactions will be investigated. Statistical significance will be set at $P < 0.05$.

The experimental sample size of 20 total horses was calculated using G*Power (version 3.1.9.6).(12) Specifically, an a priori power analysis was conducted using the CT-based pixel density between unicortical and propagating condylar fractures, as reported by Posukonis et al.(10) The power analysis resulted in a recommended sample size of 19 cases, with an effect size of 0.995, and a power of 0.9, using a 95% confidence interval. An additional case (i.e., a total of 20 horses) was added to increase statistical strength for comparison.

Potential pitfalls – Given the exploratory nature of this study and natural variation in horses and condylar fracture etiologies and configurations, type II error (i.e., accepting that there is no relationship between subchondral bone and articular cartilage when a relationship truly exists) is possible. However, given what has been previously published about condylar fractures and the consistent clinical caseload at New Bolton Center, it is expected that some relationship will be detected if a true one exists—even if data only approach significance—and these data will provide additional insight for future studies. Outcomes of this study will directly impact the clinical understanding of the relationship between subchondral bone and articular cartilage and may help in providing a more accurate prognosis for racehorses with condylar fractures at the time of surgical intervention.

Project relation to TERF mission – The TERF mission focuses on the health and welfare of Thoroughbred racehorses through research with the ultimate goal of improving racing safety. The proposed project directly addresses this mission as condylar fractures are the most common long-bone fracture in the Thoroughbred racehorse and cause notable morbidity or mortality for the racehorse. Continued efforts to understand the etiopathogenesis and prognosis for condylar fractures will directly impact the understanding of the biological relationship between the articular cartilage and subchondral bone, as well as allow clinicians to accurately treat and prognosticate when these injuries do occur. Results from this study may suggest patterns of change within the subchondral bone that are observed with condylar fractures as detected with CT, which in turn may support early detection of injuries preceding fracture development.

Impact on health and welfare of the horse – The proposed project aims to benefit Thoroughbred racehorses by expanding the current understanding of the relationship between the subchondral bone and articular cartilage tissues in horses with clinical condylar fractures; and how injuries in one—or both—tissues may affect the long-term outcome and potential for returning these horses to racing. The ultimate goal of this research is to use this increased knowledge to develop more targeted interventional

strategies to prevent fracture formation, and rehabilitation efforts for affected horses to allow them to ideally return to racing, or some level of athletic use.

--- 4. Provide a timeline detailing the expected progress of the project and specific milestones. ---

Months 1-12: Case enrollment; concurrent arthroscopic image grading Months 5-6, 11-12: CT imaging data analysis Months 10-12: Statistical analysis Month 12: Abstract and manuscript preparation

--- 5. Provide a detailed budget for the projected use of the funds. (Note: no funds will be provided for administrative overhead or capital spending; TERF reserves the right to modify funding based on Foundation requirements). Attach budget to submitted proposal as needed. ---

Personnel Salary

- No funds requested

Procedures

- Arthroscopy: \$500/horse * 20 total horses; subtotal: \$10,000

Imaging

- Computed tomography (CT): \$500/horse * 20 total horses; subtotal: \$10,000

Total requested budget: \$20,000

Budget Justification

Personnel

Drs. Holly Stewart (PI), Jose Garcia-Lopez (Co-I), David Levine (Co-I), and Kyla Ortved (Co-I) are board-certified veterinary surgeons. They will all be directly involved in case enrollment and arthroscopic evaluation of affected horses. Dr. Stewart is the principal investigator and has surgical and CT imaging expertise. Dr. Stewart will be involved in all aspects of this project, including imaging, surgical treatment, lesion grading, patient outcome follow-up, data interpretation and statistical analyses, and manuscript preparation.

Dr. Kathryn Bill (Co-I) is a board-certified veterinary radiologist with secondary certification in equine diagnostic imaging. She has extensive experience in CT imaging and will be involved in imaging protocol development and image interpretation.

Procedures

Arthroscopy: Arthroscopic evaluation of the metacarpo/tarsophalangeal (fetlock) joints of horses with condylar fractures will be performed under the same anesthetic episode as fracture repair. Costs associated with the use of all arthroscopic equipment, including arthroscopic camera, arthroscopic video tower, sterile fluids, and suture, as well as additional anesthesia procedural time are included in this price. \$500/arthroscopy, 20 horses; Total: \$10,000

Imaging

Computed tomography (CT): Operational costs for the patient-side, fan-beam CT are reflected in this price, and include a total of one CT scan of the condylar fracture and associated metacarpo/tarsophalangeal (fetlock) joint. CT scans will be performed under the same anesthetic

episode as fracture repair, and stored in a DICOM format for later image analysis. \$500/CT scan, 20 horses; Total: \$10,000

--- 6. Provide a list of all other sources of funding and the amount(s) received. ---

None

--- 7. Briefly summarize your charity's past public education and research efforts. ---

Not applicable

--- 8. If you received funding from TERF previously, describe how these funds were used and outcomes achieved. Include any relevant publicity your charity received relating to the funding. (i.e.: media coverage, such as news articles, scientific publications, provide links to copies, as appropriate). ---

Dr. Holly Stewart (PI) received the 2020 Graduate Research Grant funded by The AAEP Foundation for the Horse entitled "Validation of an innovative contrast subtraction technique to detect equine bone marrow lesions using CT". This project was supported in a partnership with TERF. Although initially delayed by the COVID-19 pandemic, this project is successfully underway and is due to be completed by the end of 2023. Results from this study will be disseminated through presentations at national meetings and the submission of a manuscript to a peer-reviewed veterinary journal.

--- 9. List other organizations or major contributors that have provided funding to your organization in the last calendar/fiscal year. For research grant applications, provide a list of all current funding relating to your current proposal. ---

None

--- 10. Name a responsible person with whom TERF may communicate regarding specific questions and who will be responsible for follow-up information regarding the project. ---

Holly Stewart

--- 11. Provide appropriate references to support the proposed research. ---

1. McIlwraith CW, Frisbie DD, Kawcak CE. The horse as a model of naturally occurring osteoarthritis. *Bone Joint Res* 2012;1:297–309.
2. Lawrence R, Felson D, Helmick C, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26–35.
3. Alliston T, Hernandez C, Findlay D, et al. Bone marrow lesions in osteoarthritis: What lies beneath. *J Orthop Res* 2018;36:1818–1825.
4. Cruz AM, Poljak Z, Filejski C, et al. Epidemiologic characteristics of catastrophic musculoskeletal injuries in Thoroughbred racehorses. *Am J Vet Res* 2007;68:1370–1375.
5. Parkin TDH. Epidemiology of Racetrack Injuries in Racehorses. *Veterinary Clinics of North America - Equine Practice* 2008;24:1–19.
6. Kawcak CE, McIlwraith CW, Norrdin RW, et al. The role of subchondral bone in joint disease: a review. *Equine Vet J* 2001;33:120–126.

7. Boyde A, Firth EC. Musculoskeletal responses of 2-year-old Thoroughbred horses to early training. 8. Quantitative back-scattered electron scanning electron microscopy and confocal fluorescence microscopy of the epiphysis of the third metacarpal bone. *N Z Vet J* 2005;53:123–132.
8. Parkin TDH, Clegg PD, French NP, et al. Catastrophic fracture of the lateral condyle of the third metacarpus/metatarsus in UK racehorses - Fracture descriptions and pre-existing pathology. *Veterinary Journal* 2006;171:157–165.
9. Loughridge AB, Hess AM, Parkin TD, et al. Qualitative assessment of bone density at the distal articulating surface of the third metacarpal in Thoroughbred racehorses with and without condylar fracture. *Equine Vet J* 2017;49:172–177.
10. Posukonis MN, Daghish J, Wright IM, et al. Novel computed tomographic analysis demonstrates differences in patterns of bone mineral content between fracture configurations in distal condylar fractures of the third metacarpal/metatarsal bones in 97 Thoroughbred racehorses. *Am J Vet Res* 2022;83.

--- 12. How many Executive Staff and Board of Directors does your organization have? ---

1

--- Director Name (1) ---

<https://secretary.upenn.edu/trustees-governance/trust>

--- 1. Name - Job Title ---

Not applicable