2015 Bone and Muscle Risks Standing Review Panel

Research Plan Review for:
The Risk of Bone Fracture due to Spaceflight-Induced Changes to Bone,
The Concern of Intervertebral Disc Damage Upon and Immediately After Re-Exposure to Gravity, and
The Risk of Early Onset Osteoporosis Due to Spaceflight

Status Review for:
The Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity and
The Risk of Impaired Performance Due to Reduced Muscle Mass, Strength & Endurance

Final Report

I. Executive Summary and Overall Evaluation

The 2015 Bone and Muscle Risks Standing Review Panel (from here on referred to as the SRP) participated in a WebEx/teleconference with members of the Human Health Countermeasures (HHC) Element, the Exploration Medical Capability (ExMC) Element, representatives from the Human Research Program (HRP), NASA Headquarters, and NASA Research and Education Support Services on December 16, 2015 (list of participants is in Section X of this report). The SRP reviewed the updated research plans for the Risk of Bone Fracture due to Spaceflight-Induced Changes to Bone (Fracture Risk), the Concern of Intervertebral Disc Damage Upon and Immediately After Re-Exposure to Gravity (IVD Risk), and the Risk of Early Onset Osteoporosis Due to Spaceflight (Osteo Risk). The SRP also received an informational presentation about the Advanced Exercise Concepts (AEC) Project and lastly a status update on the Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity (Aerobic Risk) and the Risk of Impaired Performance Due to Reduced Muscle Mass, Strength & Endurance (Muscle Risk).

The SRP would like to commend Dr. Ryder for stepping in at the last minute for Dr. Ploutz-Snyder and giving the status update on the Aerobic and Muscle Risks. The AEC Project Manager, Dr. Gail Perusek was very informative and provided background information that the SRP had previously requested. As the SRP has stated in previous years, the SRP appreciates Dr. Sibonga's overview of the complex, cumulative activities regarding research in the Fracture, IVD, and Osteo Risks.

The SRP agrees with the movement of the Fracture Risk to the ExMC Element. The approach to fracture assessment and treatment by the clinical team is excellent. The SRP is pleased that the ExMC Element is ready to integrate ultrasound for bone into the overall ultrasound package.

Similar to previous SRP reports, there are several areas of concern that the SRP discussed. Since the inception of the SRP in 2009, the SRP has requested that the presentations be organized in a manner that matches the information in the Integrated Research Plan (IRP) that is the main source of material for the SRP to review. The way the information is presented makes it very difficult for the SRP to adequately address its charge and assist the HRP as effectively as possible. The SRP would like to reiterate some possible remedies to improve its ability to carry out its roles as per its charge:

- The SRP requests to see an organized summary of the high priority (vis-a-vis "likelihood and consequence" criteria) deliverables, unfinished, and planned studies that most closely address the "essential vs. good-to-know" parts of the current Bone Research Portfolio for Fracture, IVD, and Osteo Risks.
- Data should be presented in a way that easily addresses the Gaps and Tasks being reviewed. The SRP did not see any conclusions that were drawn from the data and related to task completion that makes it very hard to assess. Some of the data were presented graphically, but conclusions and application to the Gaps were not clearly described. In many cases the SRP was left to apply the data to the Gaps rather than have the information presented to them.
- Finally, as stated in the 2014 SRP Bone and Muscle Risks final report, the SRP requests reports from all other workshops/summits, as well as reprints of important research publications supported by NASA, as they become available.

II. Critique of Gaps and Tasks for the Risk of Bone Fracture due to Spaceflight-Induced Changes to Bone (Fracture Risk)

A. Have the proper Gaps been identified to mitigate the Risk?
   a. Are all the Gaps relevant?
   b. Are any Gaps missing?

B. Have the gap targets for closure been stated in such a way that they are measureable and closeable?
   a. Is the research strategy appropriate to close the Gaps?

C. Have the proper Tasks been identified to fill the Gaps?
   a. Are the Tasks relevant?
   b. Are there any additional research areas or approaches that should be considered?
   c. If a Task is completed, please comment on whether the findings contribute to addressing or closing the Gap.

D. If a Gap has been closed, does the rationale for Gap closure provide the appropriate evidence to support the closure?

Gaps and Tasks:

- Overall, the SRP thinks all of the Gaps are relevant and appropriate.
- The SRP hopes that the transfer of the Fracture Risk from HHC to ExMC does not mean that the SRP will be precluded from review of the data regarding any sustained in-flight fractures and circumstances surrounding such events, especially information that would provide powerful guidance for future research, such as the type of loading associated with the fracture, extravehicular activity (EVA), and other gaps previously identified.

Fracture 1: We don't understand how the space flight environment affects bone fracture healing in-flight.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Fracture Healing in Haversian Bone under Conditions of Simulated Microgravity – PI: Christian Puttlitz, Ph.D. – Colorado State University
- Extent, Causes, and Countermeasures of Impaired Fracture Healing in Hypogravity – Completed Task

- Combined Scanning Confocal Ultrasound Diagnostic and Treatment System for Bone Quality Assessment and Fracture Healing – Completed Task
- A Scanning Confocal Acoustic Diagnostic System for Non-Invasively Assessing Bone Quality – Completed Task
- Whole Joint Health: Investigating Modeled Spaceflight Changes in Mice (Postdoctoral Fellowship) – PI: Anthony Lau, Ph.D. – University of North Carolina at Chapel Hill

Fracture 2: We need to characterize the loads applied to bone for standard in-mission activities.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Bone Turnover Model: Initial Implementation – Completed Task
- Fracture Healing in Haversian Bone under Conditions of Simulated Microgravity – PI: Christian Puttlitz, Ph.D. – Colorado State University
- Whole Joint Health: Investigating Modeled Spaceflight Changes in Mice (Postdoctoral Fellowship) – PI: Anthony Lau, Ph.D. – University of North Carolina at Chapel Hill

Fracture 3: We need a validated method to estimate the risk of fracture by evaluating the ratio of applied loads to bone fracture loads for expected mechanically loaded activities during a mission.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Feasibility Study: QCT Modality for Risk Surveillance of Bone - Effects of In-flight Countermeasures on Sub-regions of the Hip Bone – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center
- Vertebral Compression Fracture Assessment – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center
- Vertebral Strength Analysis IIc
- Bone Fracture Model – Planned Task
- Bone Turnover Model: Initial Implementation – Completed Task
- Astronaut Bone Medical Standards Derived from Finite Element [FE] Modeling of QCT Scans from Populations Studies – Completed Task
- Digital Astronaut: Bone Remodeling Model – PI: James Pennline, Ph.D., NASA Glenn Research Center
- Vertebral strength and fracture risk following long duration spaceflight – PI: Mary Bouxsein, Ph.D., Harvard Medical School
- Flight Validation of an Integrated Nutritional, Pharmaceutical and Exercise CM – Planned Task
- Astronaut Bone Medical Standards Derived from Finite Element (FE) Modeling of QCT Scans from Population Studies and Astronauts (Phase II) – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) - 5 – Planned Task

ExMC 4.06: We do not have the capability to stabilize bone fractures and accelerate fracture healing during exploration missions.

- The SRP thinks this Gap is relevant and appropriate.

Task:

- Combined Scanning Confocal Ultrasound Diagnostic and Treatment System for Bone Quality Assessment and Fracture Healing – Completed Task
- Technology Watch – PI: Michael Krihak, Ph.D. – NASA Ames Research Center
- Development of capability to treat bone fractures – Planned Task
- Portable Quantitative Ultrasound with DXA/QCT and FEA Integration for Human Longitudinal Critical Bone Quality Assessment – PI: Yi-Xian Qin, Ph.D., SUNY- The State University of New York
- Ultrasound Fracture Diagnosis in Space – Completed Task

III. Critique of Gaps and Tasks for the Concern of Intervertebral Disc Damage upon and Immediately After Re-Exposure to Gravity (IVD Risk)

A. Have the proper Gaps been identified to mitigate the Risk?
   a. Are all the Gaps relevant?
   b. Are any Gaps missing?

B. Have the gap targets for closure been stated in such a way that they are measureable and closeable?
   a. Is the research strategy appropriate to close the Gaps?

C. Have the proper Tasks been identified to fill the Gaps?
   a. Are the Tasks relevant?
   b. Are there any additional research areas or approaches that should be considered?
   c. If a Task is completed, please comment on whether the findings contribute to addressing or closing the Gap.

D. If a Gap has been closed, does the rationale for Gap closure provide the appropriate evidence to support the closure?

Gaps and Tasks:

- The SRP understands the status of "Concern" for IVD damage, rather than Risk, due to the lack of sufficient evidence or quantifiable likelihood, but thinks more evidence is needed.
- Although disc herniation data were thought insufficient to deem it a Risk, the SRP thinks it is at least a major "Concern" (over four times ambient incidence) and requires ongoing study.
- The data presented show a trend for increased risk (~10%) associated with spaceflight. It seems that there has not been a consistent measurement of disk degeneration or herniation. The SRP would suggest continued monitoring and better statistical analysis of the current data.
- Ongoing flight study data from the IVD Workshop held in August 2015 were presented to the SRP and raised some comments. First, continued monitoring and risk analysis are recommended. Second, the value of in-flight ultrasound to monitor IVD changes was discussed. The surprising hint of compression rather than expansion raises unease about the approach. The SPR recognizes the general utility of in-flight ultrasound.
    - It is unclear to the SRP how ultrasound measurement of disc and vertebral height

are helpful/relevant? Could it be correlated with disc herniation? Can you visualize a "posterior" herniated disc with an anterior ultrasound?
    - The SRP thinks more ground-based studies of ultrasound precision, correlation between ultrasound and magnetic resonance imaging (MRI), sources of high variability, and rigorous use of power calculations are needed.
- Muscle atrophy was measured on spine MRIs on return from mission and at six months post-flight. Should longer-term data be obtained to better assess recovery? Could there be a correlation between paraspinal muscle atrophy and disc herniation?
- The SRP thinks it should be considered that all astronauts have pre-flight spine MRIs to assess existing disc problems and predisposition to symptomatic disc herniations.

IVD1: Determine whether post-flight back pain and/or injury are caused by changes to the vertebral body in-flight.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Risk of Intervertebral Disc Damage After Prolonged Spaceflight – PI: Alan Hargens, Ph.D., University of California - San Diego
- Sonographic Astronaut Vertebral Examination – PI: Scott Dulchavsky, M.D., Ph.D., Henry Ford Health System
- Disc Damage Countermeasure – Planned Task
- Disc Herniation Risk Analysis – Completed Task

ExMC 4.08: We do not have the capability to optimally treat musculoskeletal injuries during exploration missions.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Development of capability to treat musculoskeletal injuries – Planned Task
- Technology Watch – PI: Michael Krihak, Ph.D. – NASA Ames Research Center
- Risk of Intervertebral Disc Damage After Prolonged Spaceflight – PI: Alan Hargens, Ph.D., University of California - San Diego
- Sonographic Astronaut Vertebral Examination – PI: Scott Dulchavsky, M.D., Ph.D., Henry Ford Health System

IV. Critique of Gaps and Tasks for the Risk of Early Onset Osteoporosis Due to Spaceflight (Osteo Risk)

A. Have the proper Gaps been identified to mitigate the Risk?
    a. Are all the Gaps relevant?
    b. Are any Gaps missing?
B. Have the gap targets for closure been stated in such a way that they are measureable and closeable?
    a. Is the research strategy appropriate to close the Gaps?
C. Have the proper Tasks been identified to fill the Gaps?
    a. Are the Tasks relevant?
    b. Are there any additional research areas or approaches that should be considered?
    c. If a Task is completed, please comment on whether the findings contribute to addressing or

closing the Gap.

D. *If a Gap has been closed, does the rationale for Gap closure provide the appropriate evidence to support the closure?*

Gaps and Tasks:

- The SRP is very disappointed to not be provided with a tabulated summary of tasks accomplished since the 2014 SRP meeting that address the Osteo Gaps. Such a table would help the SRP fulfill its charge. Thus, the SRP cannot determine the extent of progress towards filling or closing any gaps.
- The Osteo Risk includes both risk during space travel and lifetime risk. This involves the risk of multiple flights, duration and recovery. There have been some disturbing data that suggest the early recovery after flight may be transient and the long-term impacts have not been assessed. There needs to be a differentiation between acute risk and lifetime risk.

Osteo 1: A new acceptable bone health standard using an expanded surrogate for bone health needs to be defined for the flight environment.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Developing a new bone medical standard for long-duration astronauts based on bone strength estimated by Finite Element [FE] Modeling – Completed Task
- Astronaut Bone Medical Standards Derived from Finite Element [FE] Modeling of QCT Scans from Populations Studies – Completed Task
- Feasibility Study: QCT Modality for Risk Surveillance of Bone - Effects of In-flight Countermeasures on Sub-regions of the Hip Bone – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center
- Astronaut Bone Medical Standards Derived from Finite Element (FE) Modeling of QCT Scans from Population Studies and Astronauts (Phase II) – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center

Osteo 2: What is the incidence & prevalence of early onset osteoporosis or fragility fractures due to exposure to spaceflight.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Vertebral Compression Fracture Assessment – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) – Completed Task
- Feasibility Study: QCT Modality for Risk Surveillance of Bone - Effects of In-flight Countermeasures on Sub-regions of the Hip Bone – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center

Osteo 3: We need a validated clinically relevant method for assessing the effect of spaceflight on osteoporosis or fracture risk in long-duration astronauts.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Feasibility Study: QCT Modality for Risk Surveillance of Bone - Effects of In-flight Countermeasures on Sub-regions of the Hip Bone – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center
- Vertebral Compression Fracture Assessment – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center
- Vertebral Strength Analysis II – Planned Task
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) – Completed Task
- Vertebral strength and fracture risk following long duration spaceflight – PI: Mary Bouxsein, Ph.D., Harvard Medical School

Osteo 4: We don't know the contribution of each risk factor on bone loss and recovery of bone strength, and which factors are the best targets for countermeasure application.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Epidemiologic Analyses of Risk Factors for Bone Loss and Recovery Related to Long Duration Space Flight – PI: Shreyasee Amin, Ph.D., Mayo Clinic
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) – Completed Task
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) – II – Planned Task
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) - III – Planned Task
- Nutritional Status Assessment: SMO-016E – Completed Task
- An Integrated Musculoskeletal Countermeasure Battery for Long-Duration Lunar Missions – Completed Task
- Simulated Microgravity and Radiation-Induced Bone Degeneration: Oxidative Stress- and p53-Dependent Mechanisms – Completed Task
- Space Biochemistry Profile – Planned Task
- Mouse Flight Study – Planned Task
- Retrospective Study of Serum Sclerostin Measurements in Bedrest Subjects – Completed Task
- Bone Turnover Model: Initial Implementation – Completed Task
- Contributors to Long-Term Recovery of Bone Strength following Exposure to Microgravity – Completed Task
- Recovery of Musculoskeletal Quantity and Quality upon Multiple Microgravity Exposure – Completed Task
- Space Radiation and Bone Loss: Lunar Outpost Mission Critical Scenarios and Countermeasures – Completed Task
- Maintaining Musculoskeletal Health in the Lunar Environment – Completed Task
- Pilot Studies of Radiation Damage in Organ Tissues of Mice – Completed Task
- Simulated space radiation and weightlessness: vascular-bone coupling mechanisms to preserve skeletal health – PI: Ruth Globus, Ph.D., NASA Ames Research Center
- Evaluation of a sclerostin antibody in mice as a novel promoter of bone formation during spaceflight – Completed Task

- Induction of Early Stages of Osteoarthritis After Exposure to Microgravity (NSBRI Postdoctoral Fellowship) – PI: Lilliana Mellor, Ph.D., North Carolina State University
- Contribution of the Vestibular and Sympathetic Nervous Systems to Space-Induced Bone Loss (NSBRI Postdoctoral Fellowship) – Completed Task
- Increasing the Efficiency of Exercise Countermeasures for Bone Loss – Completed Task
- Examination of Anti-Resorptive and Anabolic Treatments/Stimuli on Unloading Induced Osteoporosis – Completed Task
- Bone Recovery Potential After Bisphosphonate and PTH Treatment of Disuse Osteoporosis – Completed Task
- Integrated Regulation of Bone and Muscle Metabolism by Simulated Microgravity – PI: Henry Donahue, Ph.D., Pennsylvania State University
- Digital Astronaut: Bone Remodeling Model – PI: James Pennline, Ph.D., NASA Glenn Research Center
- Effect of Unloading on the Structure and Mechanics of Rotator Cuff Tendon-to-Bone Insertion – PI: Alix Deymier-Black, Ph.D., Washington University School of Medicine
- Assessment of Structural and Functional Knee Joint Degradation During Modeled Spaceflight – PI: Jeffrey Willey, Ph.D., Clemson University
- Sclerostin's role in regulating bone formation during long-term simulated microgravity and subsequent recovery – PI: Susan Bloomfield, Ph.D., Texas A&M University
- Skeletal Responses to Long-Duration Simulated Microgravity in Male and Female Rats – PI: Ruth Globus, Ph.D., NASA Ames Research Center
- Spinal Structure and Function after 90 Days Long-Duration Simulated Space Flight and Recovery – PI: Alan Hargens, Ph.D., University of California - San Diego
- Bone Fracture Model – Planned Task

Osteo 5: We need an inflight capability to monitor bone turnover and bone mass changes during spaceflight.

- The SRP thinks this Gap is relevant and appropriate.
- There is interest in the potential of using stable calcium isotopes to monitor bone turnover. The project funded at Arizona State University (PI: Ariel Anbar, Ph.D.) ended in November 2015. The SRP thinks more terrestrial data and method validation are needed before its potential application can be evaluated.

Tasks:

- Nutritional Status Assessment: SMO-016E – Completed Task
- Flexible Ultrasound – Correlation to Bone Measures – Planned Task
- Validation of Bone Microarchitecture Technology – Animal Study – Planned Task
- Validation of Bone Microarchitecture Technology – Ground Study – Planned Task
- Rapid measurements of bone loss using tracer-less calcium isotope analysis of blood and urine – Completed Task
- Reusable Handheld Electrolytes and Lab Technology for Humans – Completed Task
- A Scanning Confocal Acoustic Diagnostic System for Non-Invasively Assessing Bone Quality – Completed Task
- Combined Scanning Confocal Ultrasound Diagnostic and Treatment System for Bone Quality Assessment and Fracture Healing – Completed Task

- Space Biochemistry Profile – Planned Task
- In-flight Calcium Technology – Planned Task
- Data Mining for Bone Research and Clinical Advisory Panel – Completed Task (RCAP) – Completed Task
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) - II – Planned Task
- Stable Calcium Isotopes in Urine as a Biomarker of Bone Mineral Balance in Spaceflight – PI: Ariel Anbar, Ph.D., Arizona State University
- Monitoring of Bone Loss Biomarkers in Human Sweat: A Non-Invasive, Time Efficient Means of Monitoring Bone Resorption Markers under Micro and Partial Gravity Loading Conditions – Completed Task
- Lab Analysis Point-of-Care Device Evaluation and Downselect – PI: TBD
- Effects of Angiotensin Converting Enzyme Inhibitors on Bone Turnover – PI: Nahid Rianon, M.D., University of Texas Houston Health Science Center
- Integrated Resistance and Aerobic Training Study – PI: Lori Ploutz-Snyder, Ph.D., NASA Johnson Space Center
- Integrated Resistance and Aerobic Exercise Training with Small Compact Exercise Equipment – PI: Lori Ploutz-Snyder, Ph.D., NASA Johnson Space Center

Osteo 6: How do skeletal changes due to spaceflight modify the terrestrial risk of osteoporotic fractures?

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Vertebral Compression Fracture Assessment – PI: Jean Sibonga, Ph.D., NASA Johnson Space Center
- Combined Scanning Confocal Ultrasound Diagnostic and Treatment System for Bone Quality Assessment and Fracture Healing – Completed Task
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) - 5 – Planned Task

Osteo 7: We need to identify options for mitigating early onset osteoporosis before, during and after spaceflight.

- The SRP thinks this Gap is relevant and appropriate.

Tasks:

- Nutritional Status Assessment: SMO-016E – Completed Task
- Effects of Angiotensin Converting Enzyme Inhibitors on Bone Turnover – PI: Nahid Rianon, M.D., University of Texas Houston Health Science Center
- Flight Validation of an Integrated Nutritional, Pharmaceutical and Exercise CM – Planned Task
- Monitoring Bone Health by Daily Load Stimulus Measurement during Lunar Missions – Completed Task
- Pharmaceutical Countermeasure Effects on Tissue-level Quality of Immobilized Bone – Completed Task
- A Low Intensity Mechanical Countermeasure to Prohibit Osteoporosis in Astronauts During Long-Term Spaceflight – Completed Task

- Retention of Skeletal, Musculature, and Postural Status with a Non-invasive, Extremely Low-level Mechanical Signal: A Ground-based Evaluation of Efficacy – Completed Task
- Can Benefits from a Single Administration of Bisphosphonates Extend to a Second Later Exposure to Microgravity? – Completed Task
- Bisphosphonates as a Countermeasure to Space Flight Induced Bone Loss: SMO-021– PI: Adrian LeBlanc, Ph.D., USRA
- Integrated Resistance and Aerobic Training Study – PI: Lori Ploutz-Snyder, Ph.D., NASA Johnson Space Center
- Integrated Resistance and Aerobic Exercise Training with Small Compact Exercise Equipment – PI: Lori Ploutz-Snyder, Ph.D., NASA Johnson Space Center
- Data Mining for Bone RCAP - IV – Planned Task
- Data Mining for Bone Research and Clinical Advisory Panel (RCAP) - 5 – Planned Task

V. Discussion on the strengths and weaknesses of the IRP and identify remedies for the weaknesses, including answering these questions:

A. Are the Risks addressed in a comprehensive manner?
   - The SRP thinks the Risks are addressed in a comprehensive manner.

B. Are there areas of integration across HRP disciplines that are not addressed that would better address the Fracture, IVD, and Osteo Risks?
   - The Fracture Risk team should stay abreast of the research done by the Risk of Injury from Dynamic Loads (OP Risk) team. It is important to remain informed of the extreme loads expected during spaceflight. These loads should consider EVA, landing and other predictable loads that exceed daily spaceflight activity. This will be important for assessing the muscle/bone loads for training programs and for fitness for duty requirements. Load expectations have been a gap for multiple reasons and the SRP needs to understand the range of loads to maintain an integrated approach to health.

VI. Evaluation of the progress on the Fracture, IVD, and Osteo Risks Research Plans since the 2014 SRP meeting

- The SRP considers the teleconference format to be a suboptimal way to perform its annual duties as outlined in its charge. The study design, data, analysis and any conclusions were all presented so fast that there was no time for the SRP to interpret the data relative to the Gaps. In the future, the SRP would like the key data presented and secondary data summarized in tables. **There needs to be a simple presentation of the association between Gaps and task results so that there can be a discussion of what is needed, if anything, to close Gaps or parts of Gaps.**
- The SRP has no way to determine the fate of the research suggestions made after its 2013 or 2014 SRP Bone and Muscle Risks final reports. Those suggestions highlighted research approaches the SRP recommends as highest priority. They included the following:
  - The SRP acknowledges the problem of longer duration missions and the unknown

course of bone loss. It is not known whether bone loss would plateau or accelerate or stay constant. Comprehensive data from 12-month missions will add to this knowledge base, even with a small numbers of subjects.

- The SRP supports monitoring astronauts and age-matched controls by qCT and looks forward to evidence testing whether or not qCT provides better assessment of fracture risk than does DXA with FRAX or similar tools.
- The SRP supports tasks addressing the efficacy of Reclast infusion to mitigate the rate of bone loss.
- The SRP supports the need for biomarkers of bone loss, stress, inflammation, etc., that should be tested during spaceflight, for example, with saliva and emerging point-of-care technologies.

VII. Additional Comments regarding the Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity (Aerobic Risk) and the Risk of Impaired Performance Due to Reduced Muscle Mass, Strength & Endurance (Muscle Risk) Status Reviews

The SRP received two rather brief presentations regarding the Aerobic and Muscle Risks on results from previous studies and the modification of plans for future long-duration missions. New data were reported on the atrophy of cervical and lumbar paraspinal muscles with discussion focusing on the integration of bone and muscle response affecting the function of the spine. Change in vertebral body loads as a function of muscle atrophy was discussed and the SRP agrees that these experiments could support further experimental hypotheses integrating bone and muscle function in the spine. Results such as these appear to address major concerns related to bone and muscle loss, potential exercise interventions to attenuate these losses and capitalizing on the integrative nature of bone and muscle physiology in an integrated system response to prolonged exposure to microgravity.

A second observation focused on the current lack of information from the Advanced Resistive Exercise Device (ARED), something the SRP discussed last year, and the development of smaller loading systems requisite to the success of future missions where smaller payloads are required. The researchers at JSC are making some progress in developing smaller exercise devices in an environment where consistent reliable information on task specific loading is minimal. Development of exercise protocols and interventions is important as NASA moves forward to address emerging gaps in knowledge and appropriate tasks to resolve these issues that will require the combined expertise of JSC and the SRPs. The SRP encourages the JSC researchers to continue their interaction/integration between research teams and to increase the frequency of updates on progress in these projects to the SRP.

Comments specific to the Aerobic Risk Status Review:

- While current countermeasure hardware has markedly improved, vehicle constraints for future exploration are not able to accommodate the size and mass of the International Space Station (ISS) devices. This presents a major challenge to future device development related to maintaining crew health and safety. Prototype exercise devices are validated in ground-based studies and space analogs, but then handed off to other programs for flight development. The SRP considered this to be a major challenge

dictating the need for modified tasks to address new gaps in knowledge related to in-flight exercise programs.

- The SRP felt the Multi-Purpose Crew Vehicle Program (MPCVP) must be continued to develop the miniature aerobic/resistance technology that are planned to be part of the Mars transit capsule (supported in slides 7 and 9 of Dr. Perusek's presentation).
- An additional suggestion is to engage University-based engineering programs through an open invitation to compete and stimulate ideas/designs above what has been proposed thus far by NASA. As such, the engineering and scientific community would be stimulated to help NASA with this challenge.
- Information was presented primarily on AECs and MPCV devoted to the ongoing maturation of device technology such as the technology needed for Mars transit. Again, a preliminary acknowledgement of an emerging challenge.
- A rationale for the MPCV exercise protocols was presented with a focus on "Unknowns" and "Knowns" that was followed by a list of recommendations for future flights. The SRP agrees with the four recommendations proposed by Dr. Perusek.
- The SRP further proposes additional data mining regarding details of the exercise schedules followed on the ISS and MIR. The SRP suggests that in-flight exercise should be mandatory and not an "option." This should be clearly stated during the astronaut recruitment phase.
- There was brief mention made regarding current MPCV requirements for exercise. The purpose of a new MPCV Exercise device is to maintain sufficient fitness levels that are adequate to perform such tasks as emergency egress for missions that last up to 21 days.

Comments specific to the Muscle Risk Status Review:

- New preliminary data on IVD research showed atrophy in both cervical (17%) and lumbar (14%) paraspinal muscles. At R+45 days however, there was a 67% functional cross sectional area (CSA) recovery in the lumbar paraspinal muscles and a 21% functional CSA recovery in cervical extensor muscles. SRP concerns focused on several issues: variability of the data across participants and regions of the spine that might be related to sex differences, pre-flight fitness levels and workload profiles across participants. The SRP recommends these measurements continue with a focus on functional significance and implications (e.g., asymmetric loading of vertebral bodies) that might contribute to spine straightening and back pain reported by the astronauts. The SRP also suggests the experiments focus on observed differences between the anatomic and functional implications of the changes observed in cervical and lumbar paraspinal muscles in response to prolonged exposure to microgravity. Do the two regions generally experience similar atrophy in paraspinal muscles and are the changes in spine alignment and function possibly related to the amount of atrophy across regions?
- As these data include results of a microgravity intervention for both muscle and bone and the loading relationships between these two systems/tissues, the SRP strongly encourages continued work on this issue. Further to this, the SRP restates the significance of resistance training greater than 80% of one-repetition-maximum (1 RM) and that it be continued as part of any intervention (probably in the development of pre-flight fitness levels); it provides the needed intensity for top down physiological readiness for physiological function.
- As in-flight training programs are developed utilizing miniature resistance and aerobic

training devices, greater emphasis is placed on pre-flight training. This was not discussed in the brief report presented by Dr. Ryder. The SRP suggests greater focus on this period of training. Also, muscle activity in an appropriate exercise intervention dictates bone effects. These two systems directly interact mechanically and physiologically. As one changes during prolonged exposure to microgravity the other system is affected as well. These two systems are not independent of one another. The SRP strongly suggests that fundamental consideration of both systems continues as new in-flight interventions are designed capitalizing on already developed pre-flight levels of fitness.

- The SRP appreciates the response they received to their questions (sent December 21, 2015) from Dr. Ploutz-Snyder on January 8, 2015. The majority of the questions included comments on the limited data obtained from this ongoing study that precludes the development of any significant conclusions at this time. Dr. Ploutz-Snyder stated her support for a continued dialogue directing these experiments to respond to the questions posed by the SRP.
- In direct response to the question raised on slide 8 of Jeff Ryder's presentation, the SRP recommends that a muscle specific research gap related to the cervical, thoracic and lumbar spine musculature and vertebrae be added with subsequent development of appropriate countermeasures for in-flight mitigation of muscle atrophy and bone loss.
- The increase in fatigability of the back muscles, as measured with the Biering Sorensen Test, averaged 28%. However, the SRP appreciates that these data comprise limited numbers of subjects with large variability between individuals.
- A summary of exercise flight studies including ARED Kinematics (ARED Kinematics, PI: G. Ferrigno) and Sprint (Integrated Resistance and Aerobic Training Study, PI: Ploutz-Snyder) and in-flight evaluation of loads using the XSENS Force Shoes (In-flight Demonstration of Portable Load Monitoring Devices-Phase I: XSENS ForceShoe^{TM}, PI: A. Hanson) were presented. The XSENS can now measure (calculate?) ARED loads, provide a system to continuously monitor load, and provide data on exercise "form" and human system response. These studies are considered valuable and will provide information regarding human system loading during a variety of tasks that is needed to inform the development of future interventions/protocols to maintain crew health and addressing the two major risks originally posed to the SRP. As only one pair of shoes seems to be operable the SRP recommends additional XSENS force shoes be made available to the crew.
- Information on other ARED load-monitoring options; bed rest studies; the effectiveness of SPRINT in mitigating loss of bone, muscle and aerobic capacity; recently completed tasks regarding pre-flight exercise tests and prediction of performance during EVAs; a follow-up study to the previously National Space Biomedical Research Institute (NSBRI) funded study on the flywheel exercise device related to the design of a single small multi-function device to replace the CFT70 exercise suite and a list of current solicitations from NASA and the NSBRI were briefly presented.

VIII. 2015 Bone and Muscle Risks SRP Research Plan Review: Statement of Task for the Risk of Bone Fracture due to Spaceflight-Induced Changes to Bone, the Concern of Intervertebral Disc Damage Upon and Immediately After Re-Exposure to Gravity, and the Risk of Early Onset Osteoporosis Due to Spaceflight

The 2015 Bone and Muscle Risks Standing Review Panel (SRP) are chartered by the Human Research Program (HRP) Chief Scientist. The purpose of the SRP is to review the Risk of Bone Fracture due to Spaceflight-induced Changes to Bone, the Concern of Intervertebral Disc Damage upon and immediately after re-exposure to Gravity, and the Risk of Early Onset Osteoporosis Due To Spaceflight sections of the current version of the HRP's Integrated Research Plan (IRP) which is located on the Human Research Roadmap (HRR) website (http://humanresearchroadmap.nasa.gov/). Your report, addressing each of the questions in the charge below and any addendum questions, will be provided to the HRP Chief Scientist and will also be made available on the HRR website.

The 2015 Bone and Muscle Risks SRP is charged (to the fullest extent practicable) to:

1. Based on the information provided in the current version of the HRP's IRP, evaluate the ability of the IRP to satisfactorily make progress in mitigating the Risk by answering the following questions:

   A. Have the proper Gaps been identified to mitigate the Risk?
   i) Are all the Gaps relevant?
   ii) Are any Gaps missing?

   B. Have the gap targets for closure been stated in such a way that they are measureable and closeable?
   i) Is the research strategy appropriate to close the Gaps?

   C. Have the proper Tasks been identified to fill the Gaps?
   i) Are the Tasks relevant?
   ii) Are there any additional research areas or approaches that should be considered?
   iii) If a Task is completed, please comment on whether the findings contribute to addressing or closing the Gap.

   D. If a Gap has been closed, does the rationale for Gap closure provide the appropriate evidence to support the closure?

2. Identify the strengths and weaknesses of the IRP, *and* identify remedies for the weaknesses, including, but not limited to, answering these questions:
   A. Is the Risk addressed in a comprehensive manner?
   B. Are there areas of integration across HRP disciplines that are not addressed that would better address the Risk?
   C. Other

3. Based on the updates provided by the Element, please evaluate the progress in the research plan since the last SRP meeting.

4. Please comment on any important issues that are not covered in #1, #2, or #3 above, that the SRP would like to bring to the attention of the HRP Chief Scientist and/or the Element.

Additional Information Regarding This Review:

1. Expect to receive review materials at least four weeks prior to the WebEx conference call.

2. Participate in a WebEx conference call on December 16, 2015 at 12:30 pm ET.
   A. Discuss the 2015 Bone and Muscle Risks SRP Statement of Task and address questions about the SRP process.
   B. Receive presentations from the HRP Chief Scientist (or his designee), the Human Health Countermeasures (HHC) Element, and participate in a question and answer session, and briefing.

3. Prepare a draft final report (approximately one month after the WebEx conference call) that contains a detailed evaluation of the current IRP specifically addressing items #1, #2, and #3 of the SRP charge. The draft final report will be sent to the HRP Chief Scientist and he will forward it to the appropriate Element for their review. The HHC Element and the HRP Chief Scientist will review the draft final report and identify any misunderstandings or errors of fact and then provide official feedback to the SRP within two weeks of receipt of the draft report. If any misunderstandings or errors of fact are identified, the SRP will be requested to address them and finalize the 2015 SRP Final Report as quickly as possible. The 2015 SRP Final Report will be submitted to the HRP Chief Scientist and copies will be provided to the HHC Element and Exploration Medical Capability (ExMC) Element which sponsors the bone risks and also made available to the other HRP Elements. The 2015 SRP Final Report will be made available on the HRR website (http://humanresearchroadmap.nasa.gov/).

IX. 2015 Bone and Muscle Risks SRP Status Review: Statement of Task for the Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity and the Risk of Impaired Performance Due to Reduced Muscle Mass, Strength & Endurance

The 2015 Bone and Muscle Risks Standing Review Panel (SRP) will participate in a Status Review that will occur via a WebEx/teleconference with the Human Research Program (HRP) Chief Scientist (or designee) and members of the Human Health Countermeasures (HHC) Element. The purpose of this review is for the SRP to:

1. Receive an update by the HRP Chief Scientist (or designee) on the status of NASA's current and future exploration plans and the impact these will have on the HRP.

2. Receive an update on any changes within the HRP since the 2014 SRP meeting.

3. Receive an update by the Element or Project Scientist(s) since the 2014 SRP meeting.

4. Participate in a discussion with the HRP Chief Scientist (or designee) and the Element regarding possible topics to be addressed at the next SRP meeting

The 2015 Bone and Muscle Risks SRP will produce a report/comments from this status review within 30 days of the 2015 update. These comments will be submitted to the HRP Chief Scientist and copies will be provided to the HHC Element that sponsors the muscle discipline and also made available to the other HRP Elements. The 2015 SRP Final Report will be made available on the Human Research Roadmap public website (http://humanresearchroadmap.nasa.gov/).

X. Bone and Muscle Risk SRP Evidence Review WebEx/Teleconference Participants

SRP Members:
Julie Glowacki, Ph.D. (co-Chair) – Brigham and Women's Hospital
Robert Gregor, Ph.D. (co-Chair) – University of Southern California
Diane Cullen, Ph.D. – Creighton University
Almond Drake, M.D. – ECU Brody School of Medicine
Roger Enoka, Ph.D. – University of Colorado
Edward Hanley, M.D. – Carolinas Medical Center
Peter Raven, Ph.D. – University of North Texas Health Sciences Center at Fort Worth
D. Rick Sumner, Ph.D. – Rush Medical College

NASA Johnson Space Center (JSC):
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Yael Barr, Ph.D.
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Kerry George
Andrea Hanson
Beth Lewendowski
Linda Loerch
Kerry McGuire
Patty Meyer
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Peter Norsk, M.D.
Michele Perchonok, Ph.D.
Stephanne Ploeger
Jeff Ryder, Ph.D.
Mark Shelhamer, Sc.D.
Jean Sibonga, Ph.D.
Scott Smith, Ph.D.
Jennifer Villareal, Ph.D.

NASA Headquarters (HQ):
Bruce Hather, Ph.D.

NASA Space Biomedical Research Institute (NSBRI)
Tracy Johnson, Ph.D.

NASA Research and Education Support Services (NRESS):
Tiffin Ross-Shepard

XI. 2015 Bone and Muscle Risks Standing Review Panel Roster

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