Directed Research in Bone Discipline:
Refining previous research observations for space medicine.

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Lead, Bone Discipline
Human Research Program [HRP]
Johnson Space Center, Houston, TX
February 10, 2015
Directed Studies

• HRP Unique Processes, Criteria, and Guidelines (UCPG) – “Research tasks that are initiated without being competed ... awarded directly to Principal Investigators (PIs) with the requisite skills to accomplish the work.”

• Criteria: a) insufficient time for solicitation; b) highly constrained research.

• Choice by Bone Discipline Lead
• Building upon research data -- to meet aggressive schedule for Path to Risk Reduction [PRR]
Notably,

• Perceived refinements are not from SD - Space and Clinical Operations and not from SK investigators, per se.

• Translation of research data to SD previously attempted by team of SK investigators 2007 – 2009

• As Bone Risk Custodian convened a Bone Summit in 2010 – panel of osteoporosis experts – to address clinical risk management
Skeletal Health in Long-Duration Astronauts: Nature, Assessment, and Management Recommendations from the NASA Bone Summit

Eric S Orwoll, Robert A Adler, Shreyasee Amin, Neil Binkley, E Michael Lewiecki, Steven M Petak, Sue A Shapses, Mehrsheed Sinaki, Nelson B Watts, and Jean D Sibonga
Use of the Research Clinical Advisory Panels [RCAP] to prioritize NASA’s Human Research for Bone Risks

Evidence Base – Flight and Ground
• Science
• Clinical
• Operational experience

Risks

Gaps

Exploration Missions & Architectures

NASA Spaceflight Human System Standards

Integration Research Plan

Results and Deliverables

Solicitations & Directed Research

Closure Metrics

Clinically-relevant Research Tasks

HRP slide courtesy C. Kundrot
Adapted Sibonga 2012
Bone Summit II - Bottom Line

“Overall, NASA’s strategy of assessing relative fracture risk in astronauts by T-score BMD-based guidelines alone needs to be refined. Accurately determining the absolute fracture risk in astronauts is an ambitious goal that may never be fully realized. A concerted effort however should be made to expand NASA’s technical and scientific capabilities toward objectively assessing the factors contributing to the risk since long-duration space flight is expected to:

i) have profound and possibly irreversible bone changes that would not be adequately addressed by DXA BMD,

ii) affect other physiological systems (e.g., muscle) that determine fracture likelihood and

iii) expose astronauts to novel situations that involve a greater probability of overloading bones.”
What do we define here, to mitigate fractures.

- Peak Bone Mass
- Age-related Loss
- Menopause-induced Loss

Bone mass (g/calcium) vs. Age (yr)

Riggs BL, Melton LJ: Adapted from Involutional osteoporosis
Oxford Textbook of Geriatric Medicine
ADAPTED SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
Fracture probability dependent upon data being assessed.

1. **What & when** are surveillance measurements required for collection?

2. LTH: Bone Summit identified the lack of recovery as a critical trigger – and not just BMD.

3. OPS: probability of overloading of bones (task-related).

4. Early LTH – immediately after return (e.g., 1-3 years) related to activity level and limited test

5. NASA’s Bone Fracture Module - not sensitive to changes in BMD due to ARED exercise or Bisphosphonates – *due to large variability*.

6. Proposed – using bone strength calculated by Finite element modeling to reduce the uncertainty.
Study on Risk Surveillance: Hip QCT

- Test feasibility of QCT protocol for surveillance of identified clinical trigger (later).

- Accumulate surveillance data for development of clinical practice/intervention guidelines (QCT and FEM)

- **Research**: Demonstrate how QCT can delineate biochemical from mechanical countermeasures. “Proof of Concept” Pilot Study

Figures courtesy of T. Lang (UCSF) and D. Carter (Stanford U)
DXA vs. QCT Spine: Discordant Recovery Patterns in Astronauts After Spaceflight

aBMD – areal bone mineral density g/cm²

DXA vs. QCT Hip: Why the clinical concern?


aBMD – areal bone mineral density g/cm²

tBMD – trabecular volumetric bone mineral density g/cm³
Lower trabecular BMD of hip is an independent predictor of hip fracture in elderly men. Surveillance of mitigation and recovery is warranted – hypothesis should not be required.

QCT measures -- useful information regarding etiology of hip fracture, evaluation of hip fracture risk and possible targets for intervention.
<table>
<thead>
<tr>
<th>Loading Condition</th>
<th>Mean (SD) Pre-flight</th>
<th>Mean (SD) Post-flight</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stance</td>
<td>13,200 N (2300 N)</td>
<td>11,200 N (2400 N)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fall</td>
<td>2,580 N (560 N)</td>
<td>2,280 N (590 N)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

N=11 crewmembers

QCT + FEM has superior capabilities for estimating fracture loads

BMD accounts for 50-70% bone strength

QCT estimates fracture loads better than DXA

DD Cody: Femoral strength is better predicted by finite element models than QCT and DXA. J Biomechanics 32:1013 1999
FEM of QCT data integrates multiple factors associated with fracture for single composite number to estimate bone strength.
NASA’s Probabilistic Risk Assessments for Model for Fracture – using QCT+ FEM

Biomechanics and Mission Operations

courses.washington.edu/me598rc

Estimate of Fracture Probability

Probability of event

Probability of Fracture

Probability bone will fail to support load

Bone Loss in Space

Clinical and Engineering Characteristics of Bone Strength

Figure 2. Summary of literature survey on fracture load as a function of femoral neck BMD

Beck et. Al, 1990
Hayes, Myers, 1996 (2mm/s)
Hayes, Myers, 1996 (100mm/s)
Kukla et. Al 2002

Beck et. Al, 1990

Probability of event

Probability of Fracture

Probability bone will fail to support load

Fracture Load (N)

Femoral Neck BMD (g/cm^2)

0 0.2 0.4 0.6 0.8 1 1.2

0 2000 4000 6000 8000 10000 12000 14000 16000

Figure courtesy of J Myers; Adapted by Sibonga
Rationale late 1990’s: NASA develops standards for Crew Health Based on World Health Organization (WHO)

T-score = # Standard Deviations from Normal bone mineral density [mean BMD] of young healthy persons.
RESEARCH: Hypothetical FE Cutoffs (N or kN) for “Operating Bands of Bone Health”- i.e., are hips strong enough to account for declines due to spaceflight and to aging- to be used together with DXA BMD Standards.

Data slide courtesy of Keyak.
Clinical Validation of Innovative Technologies: Bone Disruption in Microarchitecture

Predisposed to “codfish” fx

Male Astronauts? Spaceflight Effect? The Hip?
Microarchitectural Measures of Trabeculae and of Spatial Orientation

Young Normal  
→  
Osteoporotic

“plates” TbTh  
“rods” TbTh

TbN

TbSep

Images courtesy of Ralph Müller, PhD, Switzerland

Adapted
Exploring Magnetic Resonance Technologies for Hip Bone Microarchitecture

- Virtual biopsy software (Acuitas: fineSA™)
- Easily translatable to any clinical or preclinical imaging system (No new hardware, No modifications)
- Innovative surface coils (and pulse sequences) show for MR-based assessments of trabecular structure in the proximal femur (Chang, NYUMC)

Source: www.acuitasmedical.com
To Sum, Directed Studies in Bone

• Feasibility of using QCT for fracture risk surveillance – collects data that are BMD-independent predictors of hip fracture.

• Developing a “decision-making tool” using FE modeling of hip bone strength derived from astronauts and from population studies with fracture outcome.

• Testing new technologies for bone microarchitecture that do not require ionizing radiation.
Consequence: Premature fragility fractures in astronauts due to previous exposure to spaceflight?

Cooper and Melton, 1992

SLIDE COURTESY OF Dr. S. AMIN, Mayo Clinic
DXA measurement of areal BMD $[\text{BMD}_a]$ – a inferred 3d measure from a 2d unit.

- Improved precision
- Low radiation
- Shorter scan times
- BMD measures over multiple skeletal sites
- Numerous studies: distribution of BMD in populations with fracture outcome
- Widely-applied surrogate for fracture – but for is it a good index for bone strength?
Hip QCT for surveillance: BMD changes in separate bone types, in response to countermeasures

<table>
<thead>
<tr>
<th></th>
<th>Index DXA</th>
<th>%/Month Change ± SD</th>
<th>Index QCT</th>
<th>%/Month Change ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aBMD Lumbar Spine</strong></td>
<td>1.06±0.63*</td>
<td>Integral vBMD Lumbar Spine</td>
<td>0.9±0.5</td>
<td></td>
</tr>
<tr>
<td><strong>Integral vBMD Lumbar Spine</strong></td>
<td>0.7±0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>aBMD Femoral Neck</strong></td>
<td>1.15±0.84*</td>
<td>Integral vBMD Femoral Neck</td>
<td>1.2±0.7</td>
<td></td>
</tr>
<tr>
<td><strong>Trabecular vBMD Femoral Neck</strong></td>
<td>2.7±1.9</td>
<td></td>
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</tr>
<tr>
<td><strong>aBMD Trochanter</strong></td>
<td>1.56±0.99*</td>
<td>Integral vBMD Trochanter</td>
<td>1.5±0.9</td>
<td></td>
</tr>
<tr>
<td><strong>Trabecular vBMD Trochanter</strong></td>
<td>2.2±0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.01, n=16-18


NOT detectable by DXA
Age: important risk factor for bone loss and fracture probability.

Kanis et al JBMR 9(8):1137, 1994
However, Paradigm Shift for assessing changes in Bone Strength as contributor to Fracture Risk.

• “Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality.” JAMA 2001

• Why is this?
Bone fragility is influenced by factors that are not detected by DXA BMD.

Disconnects discovered in population studies – in response to countermeasures.
How is DXA BMD used at JSC?

• Monitor skeletal health in all active and retired astronauts

• Characterize skeletal effects of long-duration spaceflight

• Evaluate efficacy of bone loss countermeasures

• Verify restored health status
However, diagnostic guidelines using areal BMD T-scores provide relative risk, but cannot predict who will fracture. Not useful when used alone.

BMD T-Score Values* Expeditions 1-25 (n=33)

*Comparison to Population Normals
DXA BMD, not T-scores, reveals changes that are unique & complex. Drives requirement for research.

Rapid (1-1.5%/mo) and site-specific BMD loss (means local regulation occurring).

<table>
<thead>
<tr>
<th>BMD Site</th>
<th>Mean Immediate Post Flight BMD (% change/month)</th>
<th>Mean Three Year Post Flight BMD (% change/month)</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted</td>
<td>Observed</td>
<td></td>
<td>Predicted</td>
</tr>
<tr>
<td>Total Hip</td>
<td>1.063 (0.05)</td>
<td>0.994 (-0.76)</td>
<td>&lt;0.001</td>
<td>1.066 (0.02)</td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>1.081 (0.11)</td>
<td>1.016 (-0.58)</td>
<td>&lt;0.001</td>
<td>1.085 (0.03)</td>
</tr>
<tr>
<td>Ultra-Distal Radius</td>
<td>0.558 (-0.05)</td>
<td>0.550 (-0.20)</td>
<td>0.12</td>
<td>0.541 (-0.08)</td>
</tr>
<tr>
<td>Mid-Shaft Radius</td>
<td>0.755 (0.19)</td>
<td>0.741 (-0.00)</td>
<td>0.04</td>
<td>0.749 (0.02)</td>
</tr>
<tr>
<td>Total Body</td>
<td>1.288 (-0.04)</td>
<td>1.262 (-0.26)</td>
<td>0.009</td>
<td>1.284 (-0.01)</td>
</tr>
</tbody>
</table>

Total BMD loss greater and persist compared to BMD changes predicted from algorithms derived from earth-based population.

Loss is variable due to multiple risk factors. Recovery is variable. Recovery is prolonged. But ARED can reduce BMD decline in hip.
However, DXA is limited as Research Tool: Does not account for changes in bone size which impacts bone strength.

<table>
<thead>
<tr>
<th></th>
<th>aBMD $\text{g/cm}^2$</th>
<th>Compressive Strength</th>
<th>Bending Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{radius}$</td>
<td>1</td>
<td>1.7</td>
<td>4</td>
</tr>
<tr>
<td>$\text{circum}$</td>
<td>1</td>
<td>2.3</td>
<td>8</td>
</tr>
</tbody>
</table>
**Densitometry & Reported Measurement**

QCT quantifies volumetric BMD

DXA reports areal BMD (aBMD)

\( \text{g/cm}^2 \) averaged for cortical + trabecular bone

QCT quantifies volumetric BMD

\( \text{g/cm}^3 \) for separate cortical & trabecular bones
Surveillance by QCT—Changes in Femoral Neck structure detected 12 months postflight

**Bone Mineral Content (g)**

**Volumetric Bone Mineral Density g/cm³**

**Minimum Cross-sectional Area cm²**

---

$P < 0.05$ with respect to preflight*, postflight*
QCT in Population Study measures changes in bone size with aging. Suggests that outward displacement of femoral neck is response to cortex thinning with age.

Bone Turnover Markers indirectly suggest a net loss in bone mass from the entire skeleton.
Exercise during Spaceflight does not mitigate urinary calcium excretion – as a biomarker for bone breakdown.

Slide courtesy of Dr. A. LeBlanc
ORIGINAL ARTICLE

Benefits for Bone From Resistance Exercise and Nutrition in Long-Duration Spaceflight: Evidence From Biochemistry and Densitometry

Scott M Smith,¹ Martina A Heer,² ³ Linda C Shackelford,¹ Jean D Sibonga,¹ Lori Ploutz-Snyder,⁴ and Sara R Zwart⁴

¹Human Adaptation and Countermeasures Division, National Aeronautics and Space Administration (NASA) Lyndon B. Johnson Space Center, Houston, TX, USA
²Department of Nutrition and Food Science, Nutritional Physiology, University of Bonn, Bonn, Germany
³Profil Institute for Metabolic Research GmbH, Neuss, Germany
⁴Division of Space Life Sciences, Universities Space Research Association, Houston, TX, USA
Changes in areal BMD--useful information, but not a fracture predictor

* Updated data since 2010 Bone Summit
Bone RCAP Recommendations (2010)

1. **Use QCT for risk surveillance data**. To detect clinical trigger recovery in hip trabecular BMD. Conduct scans Pre- Post-, 1 year, 2 years (if recovery not established at 1 y)

2. **QCT data required** to formulate recommended clinical practice guidelines – which are driven by fracture probability.

3. **Individualize risk assessments** – due to data constraints.

4. **Modify Bone crew health standards to be more relevant to LD astronaut experience**. Explore population studies with hip bone strength estimated by Finite Element analysis.

5. **Search/validate new technologies** to assess unique changes due to spaceflight, e.g., bone microarchitecture of central skeletal sites.
Investigate a new medical standard for BONE with Finite Element Modeling [FEM]: What is it and what can it tell NASA about hip fracture risk in the long-duration astronaut?
FEM – a computational tool to estimate failure loads ("strength") of complex structures - from models developed from QCT scans.


Images courtesy of Dr. J Keyak
Describing changes in hip bone strength with Finite Element Modeling/Analysis: Emerging data from population studies.


FE Strength Cutoffs* Task Group
E. Orwoll MD, S Khosla MD, S Amin MD, T Lang PhD, J Keyak PhD, T Keaveny PhD, D Cody PhD, JD Sibonga, Ph.D.

All Male Subjects
Stance Loading

Stance (N) vs Age (years)

AGES Controls
- Pre-flight
- AGES Fractures
- Post-flight

*Red, Yellow and Green Operating Bands

Data slide courtesy of Keyak.
Why Bone Microarchitecture?

• "…low bone mass and microarchitectural deterioration with a consequent increase in bone fragility with susceptibility to fracture …." Am. J. Med. 1991 Defined Contribution

• Disrupted microarchitecture is associated with vertebral compression fractures. Validated Fracture Predictor

• Bone Summit RCAP 2010: concern for rapid bone loss in astronauts and aggressive osteoclast activity disrupting bone microarchitecture --- which is not detectable by QCT. Orwoll, 2013 JBMR review
Indices of bone microarchitecture reflect changes in trabeculae size and spatial orientation – need to identify non-permissible outcome.
Integrated Research Plan for Bone Portfolio

GAP MANAGEMENT FOR OSTEO & FRACTURE
Gaps to define the changes to bone and the contribution to fracture risk.

**Osteo 1:** A new acceptable bone health standard using an improved surrogate for bone strength needs to be defined for the flight environment.  
**POLICY ON STANDARDS**

**Osteo 2:** What is the incidence & prevalence of early onset osteoporosis of fragility fractures due to exposure to spaceflight?  
**KNOWLEDGE GAP - EVIDENCE**

**Osteo 3:** We need a validated, clinically-relevant method for assessing the effect of spaceflight on osteoporosis or fracture risk in LD astronauts.  
**KNOWLEDGE GAP – ENABLING TECHNOLOGY**

**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.  
**KNOWLEDGE GAP - DATA**

**Osteo 5:** We need an in-flight capability to monitor bone turnover and bone mass changes during spaceflight.  
**MITIGATION GAP - DETECT**

**Osteo 6:** How do skeletal changes due to spaceflight modify the terrestrial risk of osteoporotic fractures?  
**MITIGATION GAP – SURVEILLANCE**

**Osteo 7:** We need to identify options for mitigating early onset osteoporosis before, during and after spaceflight.  
**MITIGATION GAP – PREVENTION & TREATMENT**

*MRIDs - refer to data from medically-required tests*  
Medical Requirements Integrated Document
Gaps to understand the Risk for Bone Fracture=Applied Loads/Bone Failure Loads

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

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

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.

B30: What are the loads applied to bone in-flight and during EVA activities and do they increase fracture risk in light of expected bone loss?

B31: Need additional information regarding hard and soft tissue healing in-flight. If impaired healing exists, what countermeasures can enhance healing?

B2: What new technologies are available for in-flight fracture diagnosis?

Exploration Medical Capabilities
Summary

- DXA BMD, as a sole index, is an insufficient surrogate for fracture.

- CPGs using BMD (both WHO and FRAX) are not specific for complicated subjects such as young, healthy persons following prolonged exposure to skeletal unloading (i.e. an attribute of spaceflight).

- Research data suggest that spaceflight induces changes to astronaut bones that could be profound, possibly irreversible and unlike age-related bone loss on Earth.

- There is a need to objectively assess factors across human physiology that are also influenced by spaceflight (e.g., muscle) that contribute to fracture risk.
Some of these objective assessments may require innovative technologies, analyses and modeling.

Astronauts are also exposed to novel situations that may overload their bones highlighting a need to integrate biomechanics of physical activities into risk assessments.

As we accumulate data, which reflects the biomechanical competence of bone under specific mechanically-loaded scenarios (even activities of daily living), BONE expects Bone Fracture Module to be more sensitive and/or have less uncertainty in its assessment of fracture probability.

Fracture probability drives the requirement for countermeasures. Level of evidence will unlikely be obtained; hence, the Bone RCAP (like a Data Safety Monitoring Board) will provide the recommendations.
Bone Summit Panel Members

- Eric Orwoll, MD
  - Endocrinology and Male Osteoporosis
- E. Michael Lewiecki, MD, FACP, FACE
  - Endocrinology, ISCD
- Neil Binkley, MD, CCD
  - ISCD, Geriatrics and Vitamin D
- Shreyasee Amin, MD
  - Rheumatology, Male Osteoporosis and Epidemiology
- Sue Shapses, PhD
  - Nutritional Sciences and Weight-loss
- Robert A. Adler, MD
  - Male Osteoporosis and Epidemiology
- Steven Petak, MD, JD, FACE
  - Endocrinology, ISCD
- Mehrsheed Sinaki, MD
  - Physical Medicine & Rehabilitation
- Nelson B. Watts, MD
  - Endocrinology, ISCD

Left to Right, Top Row down
Thank you.
Acknowledgements

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- Shreyasee Amin, M.D. (Mayo Clinic)
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- Joyce H. Keyak; Ph.D. (UC Irvine)
- Thomas F. Lang; PhD. (UC San Francisco)
- Adrian D. LeBlanc, Ph.D. (USRA)
- Jerry Myers, Ph.D. (NASA GRC)
- Robert Ploutz-Snyder, Ph.D (NASA JSC)
- Clarence Sams, Ph.D (NASA JSC)
- Richard Scheuring, M.D. (NASA JSC)
- Linda C. Shackelford, M.D. (NASA JSC)
- Scott A. Smith (NASA JSC)
- Scott M. Smith, Ph.D. (NASA JSC)
- Elisabeth R. Spector (NASA JSC)

Emily Morey-Holton, Ph.D.
David J. Baylink, M.D.
Backup Slides
Monitoring microarchitectural changes: Establish when perforation may occur. Mechanism of disruption informs countermeasure (anti-resorptive or anabolic)

Electron Microscopic Images to demonstrate mechanism of disruption ONLY
AGE-REGRESSIONS: Bone loss occurs at earlier age than expected.

## History of Bone Imaging in Space

<table>
<thead>
<tr>
<th>Phase</th>
<th>Year Range</th>
<th>Equipment/Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mercury</strong></td>
<td>1961-63</td>
<td>X-ray densitometry</td>
</tr>
<tr>
<td><strong>Gemini</strong></td>
<td>1965-66</td>
<td>SPA heel and wrist</td>
</tr>
<tr>
<td><strong>Apollo</strong></td>
<td>1968-72</td>
<td>SPA heel and wrist</td>
</tr>
<tr>
<td><strong>Skylab</strong></td>
<td>1973-74</td>
<td>SPA heel and wrist</td>
</tr>
<tr>
<td><strong>Space Shuttle</strong></td>
<td>1974-85</td>
<td>DXA, QCT, HR3DpQCT (ESA)</td>
</tr>
<tr>
<td><strong>ISS</strong></td>
<td>2000-present</td>
<td>DXA, QCT, CT of lumbar spine BMD</td>
</tr>
</tbody>
</table>

Soyuz/Salyut 1974-85
- SPA
- DPA

Mir 1974-85
- DXA whole body
- CT of lumbar spine BMD

Slide adapted from Amin, Mayo Clinic
Individual Results
Stance Loading (4 to 30% loss in strength)

Max loss 30%
Individual Results

Fall Loading (3 gain to 24% loss in strength)

Max loss 24%
ASTRONAUTS EXPOSED TO UNIQUE SET OF POSSIBLE RISK FACTORS DURING SPACEFLIGHT

- Aging
  - Muscle Atrophy
  - Ca/Nutrition/Vit D
  - Increased and unbalanced bone resorption

- Fracture
  - Skeletal fragility
  - EVA Suit
  - Exercise Loads
  - Excessive bone loading

- Low bone density
  - Impaired bone quality/Stress risers

- Increased bone loss

- Postural instability
- Kinetic Energy of Mass

- CO2; Radiation on bone marrow cells
- Fluid shifts and regional blood flow
Risk Summary

Risk Title: Risk of Bone Fracture due to Spaceflight-induced Changes to Bone*

Risk Statement: Given that space flight may induce adverse changes in bone ultimate strength with respect to mechanical loads during and post-mission, there is a possibility a fracture may occur for activities otherwise unlikely to induce fracture prior to initiating space flight.

Primary Hazard: μ-gravity

Secondary Hazard: Radiation, Closed Environment (spacecraft design),


Contributing Factors: Physiological deconditioning (e.g., visual and gait impairments) and clinical factors (e.g., nutrition and neuro-muscular declines), radiation, insufficient accommodations for occupant safety and operational tasks, and detailed mission design (mission design will be closely monitored; when such details are made available, the team will ensure sub-optimal design choices are not implemented to the detriment of human health and performance).

State of Knowledge: Fracture probability is dependent upon loading and bone strength. BMD is widely used as a surrogate for bone strength but its sole use is recognized to be insufficient for risk assessment. Extensive pre/post flight Bone Mineral Density data. ARED/T2 6 days/week exercise regimens have minimized declines in BMD, which are consistent with Permissible Outcome Limits (POL). It is important to point out that the standard POL was met before ARED/T2 were implemented on the ISS; however, this may reveal the possible inadequacy of the current standard metric, which is currently under evaluation. Changes to trabecular bone, whole bone and without pharmaceuticals

<table>
<thead>
<tr>
<th>DRM Categories</th>
<th>Mission Duration</th>
<th>LxC OPS Disposition</th>
<th>LxC Risk</th>
<th>LTH Disposition</th>
<th>LTH Risk</th>
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</thead>
<tbody>
<tr>
<td>Low Earth Orbit</td>
<td>6 Months</td>
<td>1 x 4</td>
<td>Accepted</td>
<td>Standard Refinement</td>
<td>2 x 3</td>
</tr>
<tr>
<td></td>
<td>1 Year</td>
<td>1 x 4</td>
<td>Accepted</td>
<td>Standard Refinement</td>
<td>2 x 3</td>
</tr>
<tr>
<td>Deep Space Sortie</td>
<td>1 Month</td>
<td>1 x 4</td>
<td>Accepted</td>
<td>Low Probability</td>
<td>1 x 3</td>
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<tr>
<td>Lunar Visit/Habitation</td>
<td>1 Year</td>
<td>1 x 4</td>
<td>Accepted</td>
<td>Optimize</td>
<td>2 x 3</td>
</tr>
<tr>
<td>Deep Space Journey/Hab</td>
<td>1 Year</td>
<td>1 x 4</td>
<td>Accepted</td>
<td>Optimize</td>
<td>2 x 3</td>
</tr>
<tr>
<td>Planetary</td>
<td>3 Years</td>
<td>2 x 4</td>
<td>Requires Mitigation</td>
<td>3 x 3</td>
<td>Accepted</td>
</tr>
</tbody>
</table>

Risk Disposition Rationale: Accepted for LEO/ISS missions, within standard limits. Additional data are highly desired to refine standard. Deep Space Sortie Accepted due to low probability of consequence. Lunar and Deep Space Habitation requires optimization of exercise equipment/protocol and/or use of pharmaceuticals. Planetary requires mitigation for potential operational impacts due to fracture from surface EVA and optimization for long term health due to long duration mission induced bone changes.

(*) Risk Custodian: J. Sibonga