Evidence Report:

Risk of Bone Fracture due to Spaceflight-induced Changes to Bone

Human Research Program
Exploration Medical Capabilities Element

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Table of Contents

I. PRD Risk Title: Risk of Bone Fracture due to Spaceflight-induced Changes to Bone 4
II. Context 4
III. Executive Summary 4
IV. Introduction 6
V. Evidence 12
1. Data Obtained from Spaceflight Medical Operations 12
2. Data Obtained from Scientific Investigations in Flight 13
2.1 Quantitative Computed Tomography (QCT) 13
2.2 Bone Turnover Biomarkers 13
2.3 Endocrine Regulation 13
2.4 Risk Factors for Reductions in Bone Strength 13
2.5 Probabilistic Risk Assessments 14
2.6 Analysis of Data from Long-Duration Missions (Mir and ISS) 15
3. Data Obtained from Ground-Based Studies 17
VI. Computer-Based Simulation Information 19
VII. Risk in Context of Exploration Mission Operations 22
VIII. Gaps 25
IX. Conclusions 25
X. References 27
XI. Team 34
XII. List of Acronyms 34

I. PRD Risk Title: Risk of Bone Fracture due to Spaceflight-induced Changes to Bone

Risk Statement: Given that spaceflight 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 spaceflight.

II. Context

Declines in bone mineral density (BMD) occur during spaceflight at averaged loss rates between 1-1.5% per month for normally weight-bearing skeletal sites on Earth (e.g., hip, lumbar spine, lower limbs of body). These calculations are based upon total loss in BMD, as measured by dual-energy X-ray absorptiometry (DXA) technology, in astronauts before and after a typical 4-6 month long-duration mission. Currently, there are no data validating a percentage loss in BMD as a predictor of bone fracture for a terrestrial population representing the ages of astronauts flying on long-duration missions, but declines in bone mass (as captured by BMD) are clearly a risk factor for fracture. It is unclear whether bone mineral density will stabilize at a lower level, or continue to diminish for longer spaceflights. It is also unknown if fractional gravity, present on the moon and Mars, would mitigate the loss. This level of bone loss does not create an unacceptable risk of fractures for missions in microgravity (ISS and asteroid), but missions in a fractional gravity environment or missions greater than 6 month in duration could create higher fracture risk.

The risk of fracture during a mission cannot be estimated with any level of certainty until the probabilities of overloading bones during the missions are understood. If mission-related declines in bone strength (or the failure load of bone) cannot be corrected by in- and post-mission rehabilitation, crewmembers could be at greater risk of fractures after return to Earth or any other planetary body. Bone parameters that contribute to bone strength and that accurately reflect changes in bone strength due to microgravity are necessary to frame this risk. For various spaceflight mission scenarios, with in-mission tasks and post-mission activities and in the context of other risk factors, the ability to assess the probability of fracture will help determine which mitigation strategies are optimal and how they should be employed.

III. Executive Summary

Spaceflight-induced bone atrophy is targeted to specific regions of the skeleton. Site-specific losses occur at normal (Earth) weight-bearing skeletal areas, suggesting that the regions that experience larger deficits in mechanical loading in microgravity undergo the greater reduction in bone mass. Collectively, the average decrement of pre-flight areal bone mineral density (aBMD) per month is 1-1.5%, although there is

considerable variation of loss between different skeletal sites and between different crewmembers. The time course of bone mineral loss during a typical 6-month long-duration mission has not been characterized, nor are data available for characterization for mission durations of over 6 months. Consequently, it is not known if and when the loss of bone matrix and bone mineral will eventually plateau, nor is it known if bone atrophy can be mitigated by the partial gravity environments of the moon and Mars. As dictated by terrestrial medicine, full understanding of the risk of bone fracture during a mission and later in life requires that the effects of spaceflight be evaluated with additional measurements that are beyond DXA aBMD. Consequently, the operating bands for astronaut health and performance during a mission are not fully defined (NASA 2014). It is unclear which additional measurements of bone can fully capture the effect size of spaceflight. It is not known how the spaceflight-induced changes to bone affects the strength of bone, such as the load vector that bone can resist before failure, or if bone strength can be fully recovered after return to Earth. The complexity of bone tissue requires a level of evidence that cannot be met by bioastronautics research due to the slow accumulation of biomedical data and small number of long-duration astronauts. With the lack of clinical evidence for the risk and the aggressive planning for future space exploration, research technologies and analyses may need to transition to the clinical arena under mission operation circumstances to facilitate risk definition and attempt mitigation. Given the paucity of data, statistical and computational modeling may be useful tools to understanding how changes to musculoskeletal physiology, tissue and cellular activities can influence fracture probability.

The Factor of Risk index for fracture evaluates the ratio of applied load to the failure load of bone. Consequently, the risk for fracture is minimal during missions in low Earth orbit because applied loads associated with falling, or with crushing, are essentially non-existent in a microgravity environment; those that do exist can be successfully mitigated by "engineering out" the risk with human-protective design. Mechanical loads to bone, however, may increase in the gravitational environment of planetary surfaces. Likewise, the risk increases with the performance of mission activities during exploration missions, such as the construction of habitats, ambulation in extravehicular suits, jumping from ladders or structures, conducting vehicle egresses, or off-nominal spacecraft landings. Similarly, risk increases after return to Earth with the resumption of pre-flight physical activities that may overload skeletal integrity before it is fully restored. The increased risk for bone fracture may also exist in long-term skeletal health with the cumulative effects of aging and of spaceflight-associated remodeling.

There are medical requirements to monitor the skeletal effects of long-duration spaceflight with measurements of aBMD by DXA and of biomarkers for bone turnover. Some specific types of fractures have only recently (e.g. vertebral compression) or not at all (e.g. occult stress fractures) been assessed in astronauts after return. Structural evaluations of bones using newer imaging technologies have not been measured longitudinally in the majority of astronauts. The pattern of BMD loss and recovery needs to be evaluated further on a multifactorial, cross-discipline

level. In order to identify, understand, and define the risk factors for bone fracture occurring during and after spaceflight. Additionally, bone needs to be fully evaluated with specific and expanded measures beyond BMD to capture changes to "bone quality." This is highlighted further by the most modern definition of osteoporosis as "… a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality" (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy 2001).

To summarize:

- Bone changes occur during space travel.
- Multiple factors during spaceflight (physiological and environmental) can influence bone changes
- DXA-measured areal BMD has been shown to be an incomplete indicator of whole bone strength.
- Knowledge characterizing changes in bone structure and microstructure is incomplete.
- The relative contribution of trabecular microarchitecture and bone geometry to whole bone strength is not known but the literature indicates that it could be substantial.
- Due to the multiple contributors to bone strength, the full impact of spaceflight on whole bone strength is unknown.
- The state of bone loading for different mission scenarios is not fully defined.

Hence, the risk for fracture necessitates understanding the biomechanical relationship between applied loads to bone and the strength of bone. To this aim, the research gaps and tasks associated with the Risk for Early Onset Osteoporosis assesses the condition of bone (including the technologies, the measurements, the estimations of bone strength, and the interpretations), while the gaps and tasks associated with the Risk for Fracture assesses the factors that influence applied loads exceeding bone strength resulting in fracture.

IV. Introduction

The probability of fractures is presumed to be minimal (<0.1%) during or after a mission in low Earth orbit. This perception is based predominantly upon the low to no incidence of fracture in over five decades of space travel of increasing duration, and low to no incidence of fracture in long-duration astronauts. The ability to maintain health and fitness in astronauts after spaceflights further enforces this presumption. There are a number of factors that have contributed to this perception, and not all are based upon a strong evidence base. First, significant decrements in BMD, beyond DXA measurement error, have not been detected for missions of less than 90 days. There are minimal impact forces to the body in the weightless environment and on planetary surfaces, limiting impact forces that could

lead to fracture, and NASA's bone health standards ensure sufficient pre-flight bone mineral density for hip and spine to prevent astronauts from returning below the minimum permissible outcome (T-score ≤-2.0) after spaceflight. The availability of the Advanced Resistive Exercise Device (ARED) after 2009 as well as adequate nutrition during flight have sufficiently reduced the previously observed declines in post-flight BMD measurements (Smith et al. 2012). Post-flight rehabilitation programs on Earth promote skeletal recovery and reduce the fall risk, and fractures in immediate post-mission and long-term health periods have been commonly attributed to overloading (trauma) or aging-related effects. Finally, reliance upon astronaut self-reporting of fractures or indicative symptomatology likely leads to under estimations of fracture. Thus, it is entirely possible that the assumption of low fracture risk and incidence related to long-duration flight is under supported and not entirely data-driven.

With exploration class missions aiming for the moon and beyond, the austere and remote environment, the "unknowns" of planet exploration, and the limited point-of-care capabilities may increase the severity of even a low probability medical event such as fracture. The occurrence of a fracture in a crewmember would not only jeopardize performance of mission objectives due to functionality impacts, it could also lead to medical complications which might result in significant morbidity or even loss of life. The documented effect of the weightless environment on bone cell activities could impair the healing process, increase the risk for non-union fractures, and expose the crewmember to additional complications such as sepsis or thromboembolytic clots. Therefore, it is of paramount importance to evaluate the propensity of a crewmember to fracture a bone under the conditions, including mission length and mission-critical task performance, and effects, including adaptive physiology, of a spaceflight to ensure appropriate medical capabilities are available. On-board capabilities may include in-flight interventions to prevent long-term health fractures, including premature fragility fractures associated with irreversible spaceflight-induced alterations, through mitigation of deconditioning or rehabilitation capabilities.

Evaluation of the probability of a bone fracture during a spaceflight mission requires an assessment of the relationship between two measurable parameters: the load vector experienced by a bone ("Applied Load," which includes both magnitude and direction) and the ability of the bone to resist that load vector without fracturing ("Bone Strength"). This relationship determines the "Factor of Risk." Estimating a Factor of Risk for bone fracture uses the engineering approach, often used in structure design, of calculating the "Factor of Safety," where structural failure likely occurs when the ratio of Resisting Force (strength) to Disturbing Force (stress) is <1. Factor of Risk is the inverse ratio of Factor of Safety (or the ratio of Applied Load to Bone Strength) where fracture likely occurs when the ratio >1. A simple and accurate method to determining the Factor of Risk for a bone fracture would to quantify the load required to fracture a bone. Because this approach is neither practical nor ethical, Risk for Bone Fracture integrates the research gaps and tasks

within the Risk for Early Onset Osteoporosis that describe the condition of bone and its Bone Strength.

Assessments of Bone Density in Terrestrial Medicine
A widely applied surrogate to replace the destructive calculation of a Factor of Risk is aBMD, measured by DXA. DXA is an x-ray based imaging technology with a high level of clinical utility because it is safe, available, and affordable. Because of its clinical utility, this measurement has been applied to a multitude of clinical studies substantiating its ability to predict fracture, to detect an effect size of intrinsic risk factors including menopause and aging, to generate reproducible results, and to monitor the effect of osteoporosis countermeasures. Thus, the noteworthy value of aBMD as a surrogate for fracture risk is not because it provides an accurate assessment of bone density (as true density is not areal), but because of the abundance of epidemiological data correlating aBMD with the incident fragility fractures (fractures due to osteoporosis) in population-based studies.

DXA BMD cutoff of a T-score of less than -2.5 was established for diagnosing osteoporosis in postmenopausal women based upon the detection of osteoporosis in ~30% of postmenopausal women at this score (Kanis et al. 1994). Using this cutoff, physicians can identify a clinically meaningful number of women who would be good candidates for osteoporosis therapy. In this case, aBMD is a useful index for stratifying the relative risk for fracture amongst postmenopausal, Caucasian women; however, aBMD alone is not a good predictor of who will fracture (Cummings et al. 1995). Reports in the literature have highlighted a disconnect between actual fracture incidence and calculated relative risk, as indicated by aBMD T-scores (Riggs et al. 1990; Cummings et al. 1998; Gutteridge et al. 2002; Schuit et al. 2004; Wainwright et al. 2005; Chesnut et al. 2005; Sornay-Rendu et al. 2005). The decline in the specificity and sensitivity of DXA aBMD for predicting fragility fractures may be related to the failure of aBMD to reflect a complete picture whole bone strength (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy 2001).

Given the necessity to expand measurements beyond aBMD T-scores, significant work has been put into the development of more accurate measurement tools. A meta-analysis of 12 cohorts, representing 60,000 subjects and monitoring over 250,000 person-years and 5,400 fractures, provided the basis for the FRAX calculator (Fracture Risk Assessment Tool, University of Sheffield, UK) which uses clinical risk factors with and without femoral neck BMD to determine a 10-year probability of fracture (World Health Organization 2004). However, the FRAX calculator is not recommended for use in humans under 45 years of age and does not include an important astronaut risk factor: the prolonged skeletal unloading and disuse of bone during microgravity exposure. As a result, the FRAX calculator has limited relevance to assessing fracture probability in astronauts due to spaceflight.

The limitation of aBMD as a surrogate, and the lack of a better alternative, had also been expressed in the previous evidence-based Bioastronautics Report (NASA

Human Research Program 2016). Thus, the NASA Human Research Program (HRP) supports investigations to supplement the measurement of spaceflight effects on the skeleton. Many recent and ongoing studies include novel and emerging technology in order to measure indices of "bone quality" and obtain an expanded reflection of skeletal integrity associated with spaceflight, for better predictive capability of the risk of fracture in long-duration, exploration missions.

Assessment of Bone Quality for Terrestrial Applications

One limitation of the DXA technology in its measurement of aBMD is that the index fails to account for the size and geometry of a bone. Figure 1 depicts how the bending and compressive strength of whole bone are dependent upon its size and geometry, which cannot be directly evaluated by DXA. There have been recent attempts to modify the use of DXA technology for the evaluation of volumetric or structural parameters as indices of Bone Quality (Prevrhal et al. 2004; Beck 2007) but the failure to achieve a better understanding and assessment of fracture risk above and beyond DXA measurement of aBMD (Bonnick 2007; Boudreaux and Sibonga 2015) has presumably limited their utility in the clinical arena.

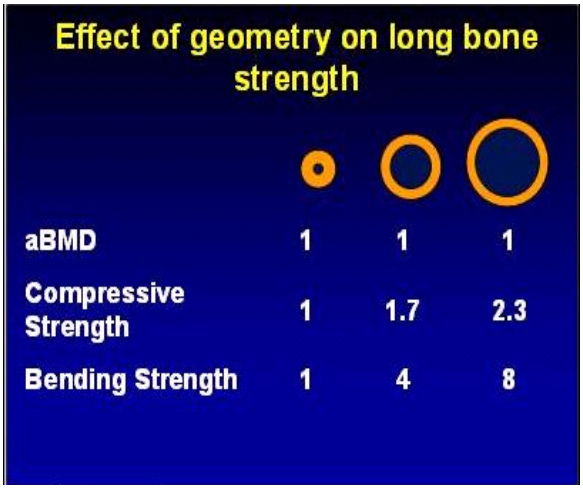

Figure 1. Mary Bouxsein, Ph.D., Bone Geometry and Skeletal Fragility. *May 2005 Bone Quality Meeting*

However, there are emerging technologies for the non-invasive assessments of other skeletal indices besides aBMD, such as other putative parameters of Bone Quality that contribute to bone strength. In particular, measurements of true, volumetric BMD (vBMD, measured in g/cm3) of whole bone and of bone compartments can be obtained by quantitative computed tomography (QCT). QCT measurements were validated in a randomized controlled trial for the prediction of hip fracture in men over 65 years old (Black et al. 2008). While the measurement of vBMD only modestly improves fracture prediction over DXA-measured aBMD, QCT enables additional measurements of the femoral neck to increase the understanding of spaceflight-induced effects on fracture risk (Black et al. 2008); that is, QCT

measurements of the femoral neck (percent cortical bone volume, trabecular vBMD, and minimum cross-sectional area) are predictors of hip fracture independent of areal BMD (Black et al. 2008). This capability is vital to understanding fracture risk in an understudied astronaut population (generally young, healthy, and predominantly male) in which bone loss is unlike age-related bone loss (Orwoll et al. 2013).

Furthermore, magnetic resonance imaging (MRI) and high-resolution QCT are emerging as novel technologies to assess changes to trabecular microarchitecture of cancellous bone at peripheral skeletal sites [HR-QCT, Scanco]. MRI-based imaging of hip trabecular microarchitecture and DXA-based vertebral microstructural analyses are being developed for microstructural assessments of the hip and spine (Hans et al. 2011; Medimaps Group 2015; Chang et al. 2015). Such measurements may be used to reflect the disruption of trabecular connectivity or degradation of cancellous bone in the bone marrow compartment of bone, as verified against parameters previously derived from bone histomorphometry (Parfitt et al. 1987). Changes to microarchitecture can influence the mechanical properties and distributions of loads in cancellous bone (van der Linden et al. 2001).

Until recently, the skeletal effects of spaceflight on bone mass had only been described by measuring aBMD determined from DXA scans performed in crewmembers before and after the typical long-duration spaceflight mission of 6 months on the International Space Station (ISS). Therefore, evaluation of Bone Quality is still required to substantiate this risk, as spaceflight represents a collection of novel risk factors that could likely affect more than areal BMD (for example, radiation effects on bone marrow). While there are multiple indices that can influence the quality of bone and whole bone strength, such as the degree of mineralization, microcrack accumulation, resorption cavities, and activation frequency, HRP needs to be focused on mature technologies in order to meet its path-to-risk reduction for an exploration-class mission. Thus, tasks that are considered essential include, first, the delivery of technologies and tests that enable non-invasive measurements of crewmembers, particularly if such technologies have been previously validated for clinical utility in terrestrial populations; and second, provision of knowledge through modeling and analog validations that can be translated directly to mission applications.

Possible Risk Factors for Falls or Injury

Age is an independent risk factor for fracture. The probability for fracture in the postmenopausal woman, for example, increases exponentially with every decade over 50 years for a given measurement of aBMD (Figure 2). Younger persons do not have the metabolic co-morbidities, the nutritional issues, or the cumulative exposure to bone loss risk factors that compound bone fragility in the elderly populations. On Earth, younger individuals also do not have the muscle loss, the postural instability, the impaired neuromuscular control and poor visual acuity that increase the risk for falling in aged persons. The integration of these clinical risk factors accounts for the increased probability for fracture in older populations as

these latter risk factors increase the propensity for falls and, accordingly, the applied loads to bone (De Laet et al. 2005). However, these contributing factors for injury may exist in astronauts deconditioned by prolonged transits beyond low Earth orbit.

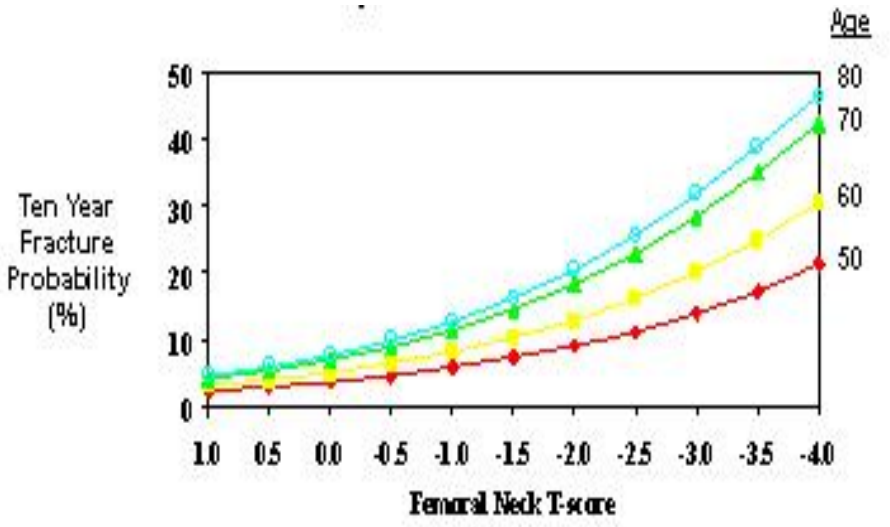

Figure 2. Age as an Independent Risk Factor for Osteoporotic Fractures. *Probability of first fracture of hip, distal forearm, proximal humerus, and symptomatic vertebral fracture in women of Malmö, Sweden. While the relative risk for fractures may be the same based upon BMD, the probability of fracture in the 50 year old is less than the probability for fracture in the 80 year old. Adapted from Kanis JA et al. Osteoporosis Int. 2001. Slide courtesy of S. Petak, M.D.*

There is an improved ability of aBMD to predict fractures when considered concurrently with clinical risk factors predisposing individuals to osteoporosis (Kanis et al. 2007). Table 1 outlines clinical risk factors associated with terrestrial osteoporosis (Espallargues et al. 2001), which are rarely observed in younger-aged, physically healthy persons of the Astronaut Corps (<55 years of age) prior to launch. However, there are risk factors for osteoporosis, as identified by Cummings (also presented in Table 1), that are more relevant to crewmembers after the typical 6-month, long-duration mission in space (Cummings et al. 1995); many of these factors are evident in crewmembers during flight and during re-adaptation to a gravitational environment. This includes the astronaut returning to their pre-flight level high physical activity soon after return to Earth with associated gait instability, imbalance, or vision impairment that may increase the falling risk soon after landing (Courtine and Pozzo 2004; Mulavara et al. 2010; Mader et al. 2011). Vitamin D deficiencies may also be a risk in crewmembers on exploration missions due to insufficient supplementation; Vitamin D deficiencies have been associated with an increased risk for falling due to the vitamin's benefit to neuromuscular coordination (Bischoff et al. 2003; Bischoff-Ferrari et al. 2004). Given the potential consequences of the fracture risk, ranging from loss of effective performance to loss of life, probability risk assessments should also consider the presence of the observed risk factors that influence the risk for falling. In addition, it may be of value to collect

kinematic measures from motion analysis and accelerometers that could be used estimate fall velocity and fall orientation while performing functional tasks in a deconditioned state (e.g., Functional Task Testing).

Table 1. Clinical Risk Factors observed in osteoporosis patient population and proposed cross-discipline risk factors relevant to long-duration crewmembers (Cummings et al. 1995; Espallargues et al. 2001).

Clinical Risk Factors for Osteoporosis (Espallargues 2001)	**Putative and Identified Risk Factors Relevant to Long-Duration and Exploration Crewmembers (Cummings 1995)**
Aging (>70y)	On Feet ≤ 4 hours per Day (reduced ground reaction forces)
Low body weight	Can't Rise From Chair Without Using Arms
Weight loss	Lowest Quartile Depth Perception
Physical inactivity	Lowest Quartile Contrast Sensitivity
Corticosteroids	Fair, Poor or Very Poor Health
Anticonvulsant drugs	Vitamin D deficiency
Primary hyperparathyroidism	Weight Loss to BW at Age 25
Diabetes mellitus (Type I)	Balance instability
Gastrectomy	Gait impairments
Pernicious anemia	Sarcopenia
Anorexia nervosa	Low sunlight exposure
Prior osteoporotic fracture	Low calcium absorption

An increased risk for fracture will be substantiated when more data are collected and uncertainty can be reduced. This report will summarize the current evidence from measurements of risk factors that influence Bone Strength and will highlight the knowledge requirements (gaps in knowledge base) in order to calculate and assess the probability for fracture during exploration missions per a NASA-developed probabilistic fracture risk assessment tool, the Bone Fracture Risk Module (Nelson et al. 2009).

V. Evidence

1. Data Obtained from Spaceflight Medical Operations

To date, the DXA measurements conducted pre- and post-flight in long-duration crewmembers have characterized deficits in aBMD for weight-bearing skeletal sites, with losses, averaged per month, that are greater than the losses detected in per year in comparable sites in elderly persons (Orwoll et al. 2013) and exceed the expected rate predicted by an algorithm derived from the a population cohort, based on serial BMD measurements of 150 men and 150 women with ages comparable (20-50 years) to the astronaut cohort (Amin et al. 2010, 2011). While declines in aBMD are a risk factor for bone fragility, the NASA tests for bone health are based upon BMD T-scores and not on percentage loss in BMD. Moreover, T-scores assess a relative risk for fragility fractures, not from fractures from the biomechanical overloading of bones, a character of fractures that are more typical of younger-aged persons (Garraway et al. 1979; Ng et al. 2012). The medical testing for

risk of fragility fractures (Sibonga 2017, figure 9) does not reveal any increased risk for fragility fractures in astronauts. A non-clinical BMD (for example, BMD for hip, spine, forearm) may "mask" a weakened bone that may strong enough to resist the mechanical loads with physical activities performed before spaceflight.

2. Data Obtained from Scientific Investigations in Flight

Although the assessment of bone integrity is incomplete, there are data in the evidence base that extend skeletal evaluation beyond DXA aBMD. While these additional measurements are not predictors of fracture per se, these measures add to the characterization of spaceflight effects that may help to define the risk. The significance of these data is summarized in sections 2.1-2.6 below.

2.1 Quantitative Computed Tomography (QCT)

The application of QCT technology provides measurements of vBMDs for whole bone and for separate bone compartments (cortical bone, cancellous bone, and combined) and three-dimensional geometry of whole bone, which can be used to assess the impact of spaceflight on whole bone strength by applying a finite element analysis (Keyak et al. 2005; Hernandez et al. 2006). The data from QCT scans conducted in long-duration crewmembers characterized how the separate compartments of the hip adapt to space differently. As described later in this report, these data were used to estimate a Factor of Risk for hip fracture on Mars, moon, and after return to Earth (Lang 2006).

2.2 Bone Turnover Biomarkers

Monitoring the changes in bone turnover markers is reported to be predictive for changes in bone mass and fracture (Garnero et al. 1999; Bonnick and Shulman 2006). Biological specimens (urine and blood) collected before, during, and after flight were evaluated after sample return to Earth. The data suggest that bone adaptation in space is driven by a predominating bone resorption that is uncoupled to bone formation (Smith et al. 2005, 2015). This perturbed bone remodeling in space suggests that there is a net loss in bone mass, albeit a biomarker for changes over the entire skeleton.

2.3 Endocrine Regulation

The human skeleton serves as mineral reservoir for maintaining calcium balance, which could be a greater issue than fractures for exploration missions exceeding a year. Studies on calcium-regulating hormones demonstrated how the endocrine regulation of calcium homeostasis can be influenced by the bone atrophy and demineralization that occurs in space (Smith et al. 1999, 2005; Sibonga 2017; Smith et al. 2015).

2.4 Risk Factors for Reductions in Bone Strength

Multiple risk factors have been identified with regards to reductions in Bone Strength. These factors include the following.

- Reduced aBMD at weight-bearing sites, a net increase in bone resorption for the entire skeleton, geometrical changes in the proximal femur, and a rapid rate of bone mineral loss collectively suggest that bones of the skeleton may

have decline in strength (LeBlanc et al. 2000a; Lang et al. 2004; Smith et al. 2005).

- Reduced cortical thickness and compartment-specific reductions in volumetric BMD in cortical and cancellous bone of hip are associated with reductions in compressive and bending strength (Lang et al. 2004) and are independent predictors of hip fracture in aged males (Black et al. 2008).
- Estimations of load capacity were assessed by analysis of models generated from QCT hip scans, performed before and after spaceflight. Significant reductions were noted in bone load capacities (minimum force to cause fracture) for applied loading with one-legged stance and posterolateral falls (Keyak et al. 2009).
- Preferential losses in trabecular bone observed in crewmembers may disrupt trabecular connectivity or reduce trabecular thickness, both of which could affect biomechanical strength of bone (van der Linden et al. 2001; Hernandez et al. 2006).
- Persistent deficits in trabecular vBMD of the hip and of lumbar spine (L1, L2) in 8 ISS crewmembers in whom a fourth scan was performed between 2-4 years after return (Dana Carpenter et al. 2010) may add to age-related declines and induce premature fragility.
- Deficiencies in vitamin D observed in long-duration crewmembers after approximately 6-month spaceflights may induce similar impairments in neuromuscular coordination and increased risk for falling as documented in the elderly (Bischoff et al. 2003; Bischoff-Ferrari et al. 2004) if in-flight supplementation for spaceflight missions beyond low Earth orbit cannot be maintained.

2.5 Probabilistic Risk Assessments

Calculating the Factor of Risk for fracture is only as accurate as the estimations of bone strength and of applied loads. Likewise, the assessment of fracture probability is dependent upon the number of factors that influence the probability of an overloading event occurring, such as the duration of the mission, the total number of EVAs conducted, the frequency of EVAs, the types of mechanically-loaded event (for example, fall impacts with high energy (such as a fall while cycling), or low energy (such as a simple trip and fall) events).

Estimations of applied load to bone are clearly not perfect. For instance, some reported algorithms to calculate loads incurred by the hip on Earth are based upon body weight; height, velocity, and orientation of falls; and dampening of force by fat padding (Robinovitch et al. 1991; Carpenter et al. 2005; Riggs et al. 2006). Both QCT and DXA data can strengthen the estimations by including measurements of soft tissue thickness over the hip (Riggs et al. 2006; Ellman et al. 2010). In addition, the factor of risk for exploration missions on a planetary surface requiring integrating the effect of partial gravity on applied loads in fractional gravity environment. These estimations may be underestimated because of the difficulty in quantifying the multi-system deconditioning of the astronauts, including factors such as vision

impairment, muscle atrophy, reduced physical fitness, and poor neuromuscular coordination. Even factors such as repetitive falling due to a cumbersome EVA suit or "loping" to ambulate in an EVA suit will increase the hazard to fractures. Other challenges may include fractional gravity influencing a proportional decline in bone mass, (Ellman et al. 2013; Swift et al. 2013) or declines in fall loads because of slower velocities and lower energy of fall impacts.

Preliminary data, including estimations of bone strength from the analysis of finite element models (Keyak et al. 2009), support the fracture risk and have been presented in a separate Evidence Base Report on Early Onset Osteoporosis (Sibonga 2017). Collectively, the risk for bones being overloaded in astronauts is more likely due to an increased probability of encountering a traumatic load because of vision impairment, loss of neuromuscular coordination, muscle atrophy, mobility issues and possibly reduced cognition or poor judgment. Risk is similarly elevated with physical activity in an unfamiliar, atypical environment, such as exploration activities on planetary surfaces with partial gravity, as well as a return to typical pre-flight physical activities, before restoration to pre-flight bone strength, after landing on Earth. To manage this risk of overloading bones, computer modeling is used to assess the probability of crewmembers encountering mechanical loads during the length of an exploration mission while performing mission tasks (Nelson et al. 2009); such modeling may also be useful for assessing risk in astronauts after return to Earth.

2.6 Analysis of Data from Long-Duration Missions (Mir and ISS)

There is a medical requirement to perform DXA measurements of aBMD in the hip, lumbar spine, whole body, forearm, and calcaneus in long-duration crewmembers to evaluate the effects of spaceflight. DXA scans were performed within 45 days prior to launch and within approximately 5 days of landing. Recovery of bone mass, as indexed by aBMD, takes considerably longer than the time to incur the loss (Vico et al. 2000; Sibonga et al. 2007). Recovery can be influenced by multiple factors such as age, nutritional intake, and post-flight activity, which may account for the restoration of BMD to pre-flight status as early as 6 months after return. Due to the complexity of bone tissue and the multi-factorial nature of bone loss, there is recognized variability in skeletal measurements in Earth-based populations. Likewise, it is not unexpected to observe highly variable responses between skeletal sites within one crewmember and between crewmembers. This variability is also evident in assays of bone turnover markers which are performed in long-duration crewmembers at similar time points before and after spaceflight missions. Biomarkers for bone resorption are reported to increase early in flight where they remain elevated until their restoration to pre-flight levels soon after return (Smith et al. 2005). Biomarkers for bone formation are not as profoundly influenced by spaceflight and are either unchanged or decreased during spaceflight; circulating levels, however, are increased approximately 1 month after landing (Smith et al. 2005).

Based upon the DXA measurement of aBMD and the World Health Organization Guidelines for Osteoporosis Diagnosis (WHO 1994), there are no data to indicate a diagnosis in astronauts after a long-duration mission (Figure 3). In other words, no long-duration astronaut has returned with a "non-permissible outcome," defined as a T-score of ≤-2.0 for the femoral neck, trochanter, or spine (NASA 2014). However, these guidelines were developed for clinicians considering interventions for perimenopausal and postmenopausal women or men over the age of 50, a target population considered to be at risk for age-related fractures. Although useful, the current aBMD-based fracture standards for risk assessment are probably not sufficient for assessing risk in astronauts who are losing bone mass by a different impact on bone remodeling (Orwoll et al. 2013).

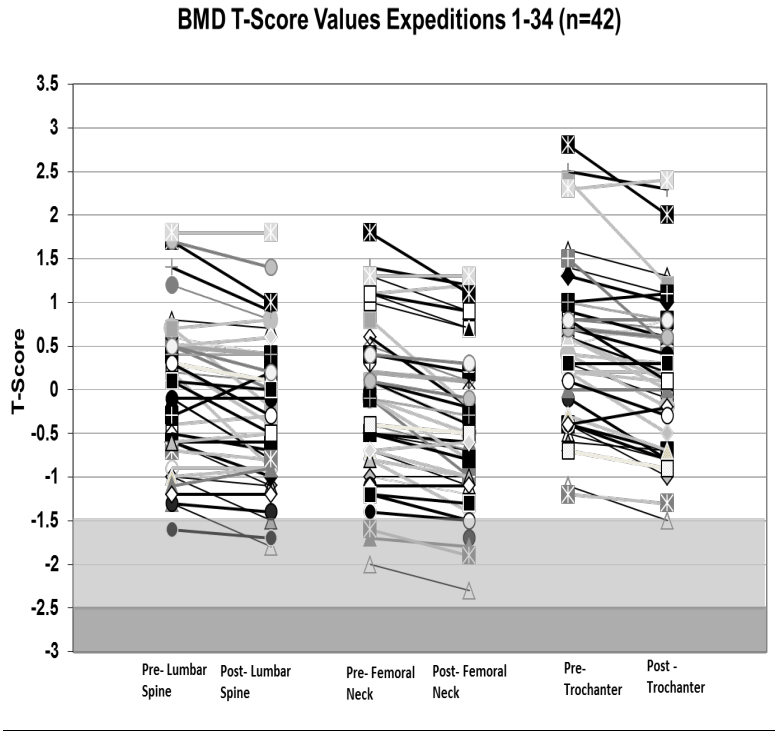

Figure 3. T-scores based upon pre-flight and post-flight measurements of BMD and references back to young white sex-matched population. No long-duration crewmember has returned from the typical 6-month mission in low Earth orbit with a diagnosis of osteoporosis according to 1994 World Health organization guidelines (WHO 1994).

More importantly, as reported in the Evidence Report for Early Onset Osteoporosis (Sibonga 2017), the average monthly BMD loss (LeBlanc et al. 2000a, 2007; Sibonga 2017) in crewmembers is almost equivalent to the annual loss of aBMD loss in comparable sites of elderly persons (Orwoll et al. 2013). This comparison of bone loss rates was also demonstrated in Table 2, which displays a comparison between the observed losses in BMD in long-duration astronauts to a predicted loss by a mathematical algorithm developed from the Rochester Bone Health Study (The Mayo Clinic, Rochester). The BMD decline in astronauts was predicted by a formula derived from a population cohort (n ~ 800) composed of subjects spanning the age

of 19-97 years (Amin et al. 2010). As mentioned above, changes in aBMD over time were derived from serial BMD measurements, which included measurements in 150 men and 150 women of ages that span the astronaut age range (20-50 years), perhaps the only population study of bone health that includes younger-aged subjects (Amin et al. 2010, 2011). The greater, calculated monthly rate of BMD loss in the younger-aged crewmembers is reminiscent of aggressive, osteoclast-driven bone resorption observed in postmenopausal women. If resorption cavities on the surface of cancellous (trabecular) bone are targeted to sites of increased stress, then cancellous bone strength and stiffness can be influenced regardless of the changes in vBMD in the cancellous bone compartment (Hernandez et al. 2006). The depth and location of resorption cavities cannot be determined non-invasively, but could be confirmed with research into options such as in vitro analyses, including histology and micro-CT, of bone samples.

Table 2. Comparison between observed BMD changes in male long-duration astronauts vs. predicted changes, immediately and approximately 3 years after return (Amin et al. 2010, 2011).

BMD Site	Mean Immediate Post Flight BMD (% change/month)			Mean Three Year Post Flight BMD (% change/month)		
	Predicted	Observed	p-value	Predicted	Observed	p-value
Total Hip	1.063 (0.05)	0.994 (-0.76)	<0.001	1.066 (0.02)	1.047 (-0.03)	<0.001
Lumbar Spine	1.081 (0.11)	1.016 (-0.58)	<0.001	1.085 (0.03)	1.069 (-0.00)	0.11
Ultra-Distal Radius	0.558 (-0.05)	0.550 (-0.20)	0.12	0.541 (-0.08)	0.551 (-0.04)	0.005
Mid-Shaft Radius	0.755 (0.19)	0.741 (-0.00)	0.04	0.749 (0.02)	0.741 (0.00)	0.28
Total Body	1.288 (-0.04)	1.262 (-0.26)	0.009	1.284 (-0.01)	1.261 (-0.05)	0.19

In addition to the risk of bone volume loss, clinical risk factors that influence the propensity for falling have been observed in crewmembers after return to Earth from long-duration missions. Losses in postural muscle mass are a contributing factor to postural instability, while assessments of head-trunk coordination suggest instability during standing and ambulation (LeBlanc et al. 2000b, a; Courtine and Pozzo 2004). Actual impairments in gait (Bloomberg and Mulavara 2003; Mulavara et al. 2010), jumping (Newman et al. 1997), and decrements in dynamic visual acuity (Peters et al. 1996; Mader et al. 2011) are evident after long-duration missions in space.

3. Data Obtained from Ground-Based Studies

There are no ground-based spaceflight analogs that have evaluated Factor of Risk for bone fracture in human subjects. There are numerous animal models (rodents, dogs, non-human primates) that immobilize or skeletally unload limbs or whole bodies as a means to induce "disuse osteoporosis." These animal models are valuable resources with which to characterize the cellular and tissue effects of mechanical unloading under well-controlled experimental conditions (Turner 2000). These models can be further applied to evaluate the efficacy of

pharmacological and mechanical countermeasures using mechanical strength testing (fracturing bones under defined loads) to quantify bone strength directly. However, as previously discussed, there are multiple physiological and biological measures that can influence whole bone strength in humans; as a result, the human skeletal effects of disuse might not be completely modeled by any single species model.

Recently, HRP funded the development of an animal model to study fracture healing and to test a rehabilitative loading protocol to promote healing in the hypogravity environment. A series of published reports described an ovine (sheep) model for fracture healing that induced the skeletal effects of simulated microgravity on the tissue of the metatarsal (Gadomski et al. 2014a) displayed delayed healing under simulated microgravity on a surgical excision (osteotomy) of the metatarsal (Gadomski et al. 2014b), and used finite element models to assess the influence of localized mechanical loading at 0.25G and 1G on fracture healing (Gadomski et al. 2016). The investigations, conducted at Colorado State University, were able to describe statistically significant tissue decrements associated with adaptation to microgravity, including a loss of bone mineral density of 29.0%, a reduction in bending modulus of 25%, and a decline in failure load of 28%. There were also decrements in parameters of bone histomorphometry (bone volume, trabecular thickness, trabecular number, formation rates and osteoblast number all declined while osteoclast number increased). Collectively, these data substantiate the overall fidelity of the sheep model to mimic the skeletal tissue effects of humans in space as well as demonstrating the utility of an external fixation device to simulate skeletal unloading on the metatarsal (Gadomski et al. 2014a). The same model was used to acquire data that suggests that locally reducing mechanical loading by varying hydrostatic pressure and stain promotes intramembranous bone formation (as opposed to endochondral ossification), which could account for the delayed healing and reduced integrity of healed fractures in a disuse environment (Gadomski et al. 2016).

There is an aggressive path-to-risk reduction for future manned spaceflight; in this context, models for probabilistic risk assessments (PRA) may be required in lieu of data that directly quantifies fracture outcomes. One NASA PRA tool has taken a biomechanical approach to assessing fracture risk by estimating the probability of overloading the skeletal bones of an astronaut. This PRA may be individualized for a specific body weight and height and for certain physical activities typical for the given astronaut. To this aim, the Digital Astronaut Project, conducted at NASA Glenn Research Center, performs a service using biomechanical algorithms to estimate the mechanical loads to the astronaut during post-mission activities. In essence, this modeling could be used to predict the ability of a deconditioned bone to resist loads incurred during performance of exploration mission objectives or after return to Earth's gravity environment. An increased fracture risk does not require a bone with osteoporosis; rather, an astronaut may be predisposed to fracture because of the asymptomatic nature of bone loss and a sub-clinical reduction in bone integrity. The

medical test, DXA 2d-measurement of aBMD T-scores, does not quantify this decline in strength.

VI. Computer-Based Simulation Information

As previously discussed, the Factor of Risk for fracture is the ratio of Applied Loads to Failure Loads, where fracture is likely to occur when the ratio is >1. The probability of fracture, on the other hand, is dependent upon multiple factors or variables. Two approaches have been used to calculate the Factor of Risk for Bone Fracture in crewmembers during and after long-duration missions. One calculation of Factor of Risk applies finite element analysis to finite element models developed from QCT scans of the hip (Keyak et al. 2005). This approach has been used to determine the Failure Load of bone (or Bone Strength) after long-duration spaceflight; for example, estimates for hip strength were determined for two loading orientations and determined for 11 crewmembers scanned at the hip by QCT (Keyak et al. 2005; Lang 2006). In recent years, merging data from terrestrial cohorts of aging populations indicate that finite element model estimates of hip strength may be related to fracture risk (Orwoll et al. 2009; Keaveny et al. 2010; Keyak et al. 2011), especially in combination with aBMD. Finite element model estimates of hip failure load quantify the ability of the hip to resist fracture for a specific load vector. This index may be the single best existing composite assessment of bone strength because of its ability to integrate applied loads with geometry and distribution of material properties, such as BMD, elastic modulus, and yield strength, in 3-D bone structure (Keyak et al. 2005). While model estimation of strength only modestly predicts fragility fracture over aBMD, the finite model does integrate multiple bone determinants of bone strength (Keyak et al. 2005). This, in conjunction with the single aBMD surrogate for bone strength, may enhance the assessment of fracture probability in each astronaut for individualized clinical decisions. This individualized approach is discussed further in the Evidence Report for Early Onset Osteoporosis (Sibonga 2017).

The other approach was developed as part of the Integrated Medical Model (IMM), a Monte Carlo simulation approach to spaceflight missions that explores the event space for medical concerns during a given reference mission. The IMM was designed to be a probabilistic model system and database of supporting medical conditions used to provide the relative risk, including likelihood and severity of outcomes, for the list of medical conditions. The associated Bone Fracture Risk Module (BFxRM) was developed at the NASA Glenn Research Center (Nelson et al. 2009), designed to estimate bone fracture probability by integrating the frequency of events, where applied loads exceeds bone strength, with physical activities of high or low energy. Specifically, the module can provide a distribution of loads to the hip based upon a fall while engaging in a range of most likely performance activities over the duration of a space mission or in the immediate post-mission time period. To predict the probability of fracture, the BFxRM takes into account the following parameters:

- Specific crewmember data (for example, age, height, body mass, initial bone mass, joint and hip fat pad stiffness, and damping characteristics)
- The duration of low-gravity exposure at any given time during the mission,
- The attenuation characteristics of the EVA suit to absorb the energy of impact (Sulkowski et al. 2011)
- The deflective strategies of the astronaut (for example, arm bracing) to protect themselves by energy reduction and limiting subsequent injury from a fall
- The specific mission parameters, including duration and transit time, and mission tasks that would lead to high levels of skeletal loading,
- The number of times that a fracture-risk event (such as a fall during EVA, impact with equipment) could occur during a mission and the details of such an event, including height or translation velocity
- The change in bone strength as a function of aBMD change (LeBlanc et al. 2000a).

To date, BFxRM estimates a distribution of applied loading, specific to the hip, per design reference missions; however, this model could be modified to assess overloading probabilities for other skeletal sites. Two primary variables are calculated in this risk analysis, including the Factor of Risk for fracture (the ratio of Applied Load to Bone Strength) and the probability that the Factor of Risk exceeds 1 (in other words, a fracture occurs) during a wide range of physical activities. To assess the probability of fracture, the frequency of overloading events and the Factor of Risk (>1) are combined and converted to a probability that is termed the "Fracture Risk Index." The frequency and types of loading events were generated by observing Apollo EVA films that documented a range of physical activities as well as cross-referencing astronaut reports. The Factor of Fracture Risk is converted to a probability of fracture from a logistic regression of actual fractures and from assumptions from the literature governing the Factor of Risk for fracture threshold. This conversion is accomplished by selecting random combinations of the factors and attributes described above, modeling via Monte Carlo simulation, and generating a probabilistic distribution for mechanical loads (kN) to the hip for ISS, lunar, and Martian missions and during post-flight activities on Earth (Nelson et al. 2009).

In the IMM, the probabilistic modeling approach provides a group mean estimate of fracture probability to the wrist, hip and lumbar spine; each of these sites was previously identified by the IMM to be at higher risk than other bony locations for overloading and risk of fracture (Nelson et al. 2009). Equally important, it provides boundaries of the uncertainty in this PRA by using data and prevailing assumptions reported in the literature. The model's metric, the probability of fracture occurrence, can be used in decision-making and planning for exploration-class missions and for comparison across all the other risks in the mission context.

The Factor of Risk levels for male astronauts during a specific EVA mission scenario on Mars and lunar missions are displayed in Table 3. For this report (Nelson et al. 2009), the Factor of Risk used aBMD data as the surrogate for bone strength.

Table 3. Mission average Factor of Risk levels for several different mission scenarios for a male astronaut on Extravehicular Activities (Nelson et al. 2009).

Activity or event	**Mission location**	**Mission duration**	**Mean Factor of Risk**	**Std**
Femoral Neck Fracture				
Fall to side	Moon	Short	0.09	0.07
Fall to side	Moon	Long	0.10	0.08
Fall to side	Mars	Short	0.23	0.16
Fall to side	Mars	Long	0.28	0.20
Lumbar Spine Fracture				
45º trunk flexion, holding a load	Moon	Short	0.12	0.03
90º trunk flexion, holding a load	Moon	Short	0.08	0.03
Fall from 1m, landing on two feet	Moon	Short	0.30	0.05
Fall from 2m, landing on two feet	Moon	Short	0.46	0.10
45º trunk flexion, holding a load	Moon	Long	0.12	0.03
90º trunk flexion, holding a load	Moon	Long	0.08	0.03
Fall from 1m, landing on two feet	Moon	Long	0.31	0.06
Fall from 2m, landing on two feet	Moon	Long	0.48	0.10
45º trunk flexion, holding a load	Mars	Short	0.29	0.08
90º trunk flexion, holding a load	Mars	Short	0.20	0.06
Fall from 1m, landing on two feet	Mars	Short	0.56	0.12
Fall from 2m, landing on two feet	Mars	Short	0.77	0.16
45º trunk flexion, holding a load	Mars	Long	0.34	0.11
90º trunk flexion, holding a load	Mars	Long	0.23	0.08
Fall from 1m, landing on two feet	Mars	Long	0.64	0.17
Fall from 2m, landing on two feet	Mars	Long	0.88	0.24

Taking into account available data to date, the Factor of Risk levels at the femoral neck are averaged and provided for several different activities during several specific mission scenarios. While no Factor of Risk for fracture exceeds 1 (indicating certain risk of fracture) for any single event, the probability of fracture will increase as the frequency of an event increases.

New spaceflight aBMD data have become available since 2009 with the use of the ARED exercise countermeasure on the ISS. The ARED provides weight-bearing exercises with up to 600 pound-force resistance which more closely simulates the lifting of free weights on Earth. This capability provides the 2-3x body weight resistance typically required to maintain bone mass (Kohrt et al. 2004). Previous to ARED, only 300 pound-force was provided by the interim Resistive Exercise Device (iRED). Consequently, resistance exercise with ARED reduced the total change in aBMD in ISS astronauts following spaceflight. Calculated rates of BMD loss (n=11 astronauts as of summer 2012) are displayed in Table 4.

Table 4. Calculated monthly loss in BMD before (LeBlanc et al. 2000a) and after ARED use on ISS.

Trochanter	**Rate of BMD Loss (%/mo) Pre-ARED Use**	**Rate of BMD Loss (%/mo) With ARED Use**
Mean	-1.56	-0.5
Standard Deviation	0.99	0.4
Minimum	-0.01	-0.07
Maximum	-3.0	-1.34
Lumbar Spine	**Rate of BMD Loss (%/mo) Pre-ARED Use**	**Rate of BMD Loss (%/mo) With ARED Use**
Mean	-1.06	-0.32
Standard Deviation	0.63	0.44
Minimum	0	-0.16
Maximum	-2.0	-1.35

VII. Risk in Context of Exploration Mission Operations

Specific exploration mission scenarios are defined according to the duration of the time in space (Table 5). The BFxRM was applied to each of these mission scenarios to determine the probability of bone fracture during the performance of specific mission activities and the duration of the specific mission (including habitation and transit time).

Table 5. Definition of Exploration Mission Scenarios by Duration

Duration	**Destination**	**Transit Time to destination (days)**	**Length of Stay (days)**	**Transit Time to Earth (days)**
Short	Moon	3	8	3
Long	Moon	5	170	5
Short	Mars	162	40	162
Long	Mars	189	540	189

Figure 4 provides a graphical illustration of the probability of bone fracture occurrence for male astronauts during various activities or events of a lunar or Martian mission. Loading events include a fall to the side, a 45 degree bend from the waist, a 90 degree bend from the waist, a drop jump from 1 meter, and a drop jump from 2 meters. Figure 4 shows that the probability of fracture is less (<0.2%) during short-duration missions to the moon, most likely due to decreased exposure time in space. It is presumed that the severity of bone loss varies as a function of time, although it is unknown if bone loss is a linear or an exponential decline. Given that the recovery of BMD after return to Earth is asymptotic (Sibonga et al. 2007), speculation is that the decline in BMD follows a similar pattern of decline. Of the activities evaluated, the probability of fracture is greater for falls to the side and for drops from 2 meters height. It can be presumed that the lower gravitational level (roughly one-sixth of Earth gravity) on the moon will mitigate bone loss likely proportionally with fractional gravity, as in a rodent model for partial weight-bearing (Ellman et al. 2013; Swift et al. 2013). The probability for fracture increases as the missions become longer (0.02% moon to 2.0% Mars) and in the higher gravity environment of the Martian surface (roughly one-third of Earth gravity).

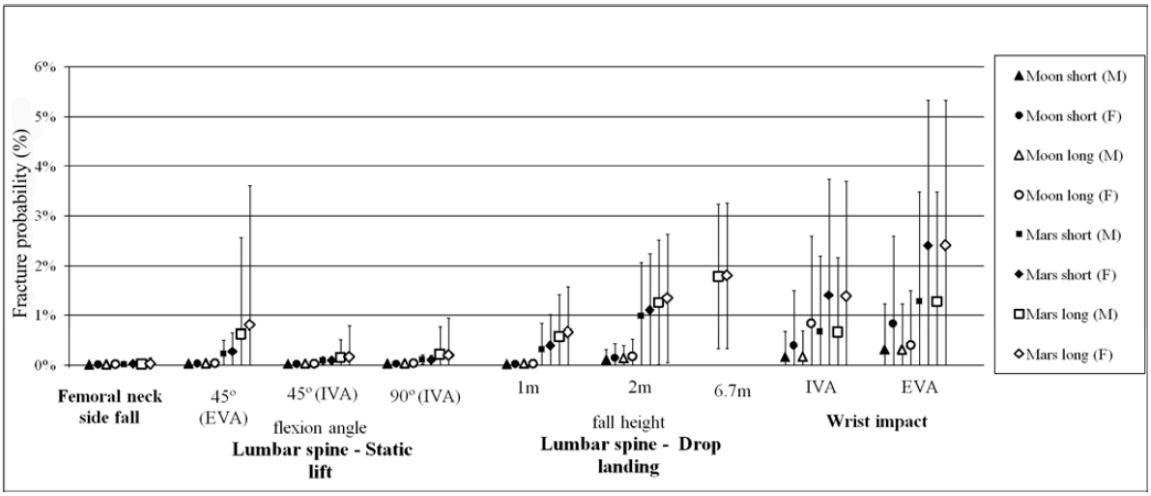

Figure 4. Probability of bone fracture for male astronauts during reference missions to the moon and Mars (Nelson et al. 2009).

As previously mentioned, a Factor of Risk had been calculated to address the impact of a Mars mission for fracture risk after return to Earth (Sibonga 2017). This estimation was based upon the QCT scans of the hip performed in ISS crewmembers (Lang 2006). The pre- and post-flight QCT data from eleven ISS subjects were analyzed by finite element modeling to determine hip fracture loads before and after spaceflight (Keyak et al. 2009). These data were used to calculate a Factor of Risk for fracture at the time of launch (pre-flight) and after return to Earth (post-flight Mars Long mission), as provided below in Table 6. These estimations indicated that crewmembers that returned back to Earth from a Mars mission would have a comparable risk of fracture on Earth to an elderly postmenopausal female, particularly for a loading condition associated with a posterolateral fall but not for forces associated with postural stance (Sibonga 2017). Again, the elderly are likely

to have additional risk factors and skeletal changes that are associated with advanced age contributing to their propensity to fracture over a younger-aged person.

Table 6. Estimated Factor of Risks based upon Finite Element Analysis of Fracture Load

	Factor of Risk: Estimated Applied Load/Fracture Load Ratio*
Astronaut pre-flight	0.89±0.21
Astronaut on Earth after Mars mission	1.07±0.30
Women, 70-80 years of age	1.04±0.37
Astronauts on Mars (0.38 G)	0.66±0.15

*a ratio >1 indicates that the applied load exceeds the fracture load (strength of the bone) and fracture will occur

The following assumptions were made in these calculations of Factor of Risk. First, the only applied forces were from gravity fields. Not only does this assumption underestimate fracture risk, but it also does not address a potential protective effect of an exoskeleton (EVA suit). The applied loads on skeleton due to suit design, EVA activities, or tasks performed on planetary surfaces are not known. Further, it was assumed that there was a consistent loss in bone mass during space travel to and from Mars based upon an estimated monthly loss of BMD, which presumes a constant loss, for weight-bearing sites. The actual time course of bone mineral loss is not known. Further, the model assumes that no further bone loss occurs during exposure to 1/6 (lunar) or 1/3 (Martian) gravity. We do not currently know the extent, if any, that these partial gravity fields will mitigate bone atrophy. Rodent studies in ground-based models of partial weight-bearing suggest that partial weight-bearing loads do not prevent (Swift et al. 2013), or proportionally reduce (Ellman et al. 2013) musculoskeletal declines.

Similar calculations of Factor of Risk can be performed for other mission scenarios as presented in Table 5. Calculations will have less uncertainty as more data reflecting changes to additional bone parameters, such as bone structure, are better defined. Bone data acquired by other modalities and analyses may improve the probabilistic risk assessments for fracture (Cody et al. 1999).

When the rate of BMD loss was changed within the BFxRM to reflect the aBMD data of crewmembers with access to ARED, with all other factors within the BFxRM remaining the same, there was minimal change in the probability of bone fracture for the six reference missions. The reason for the minimal change may be due to the following:

- The BFxRM is not sensitive to changes in aBMD. aBMD by DXA accounts for only 50-70% of actual bone strength, so a small change in aBMD translates to a small change in bone strength following ARED access, even over the course of long Martian missions. US astronauts have substantial pre-flight bone mass, with aBMD T-scores greater than average BMD of young healthy persons, and the loss of bone mass during spaceflight, though still evident even with resistive exercise on ARED, is small relative to the absolute mass.

- The lower gravitational environments on moon and Mars reduce the velocity of a fall and, subsequently, applied loads to the hip during a fall on a planetary surface.
- There is much variability with rates of aBMD loss rendering the BRxFM insensitive to changes in aBMD induced by bisphosphonates or ARED exercise. The most sensitive parameter within the BFxRM is "the number of times during a mission that an event occurs that could result in a fracture." However, it is challenging to estimate how many times an astronaut might accidently fall.

In addition, the probability of wrist fracture remains unchanged from pre-ARED implementation because the change in BMD at the wrist during the mission is zero and was not altered by use of the ARED. Therefore, with all other factors remaining the same, the change in bone loss rate after ARED became available on-orbit had very little effect on the calculated, overall bone fracture probability. This suggests that the BRxFM using aBMD for bone strength may not be useful as a tool because it cannot evaluate the effect of a countermeasure. To this aim, finite element modeling to estimate changes in Bone Strength will be investigated in the BFxRM to improve our ability to estimate fracture probability.

VIII. Gaps

At the time of writing, 3 research knowledge gaps have been identified that are directly related to the Risk of Bone Fracture. These are:

- 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.

IX. Conclusions

A high risk for fracture is a characteristic of osteoporosis, which is a consequence of the losses in bone mass and in structural deterioration. The distinction between the increased bone fracture risk in persons with osteoporosis and the increased risk for fractures during a spaceflight mission is based upon a Factor of Risk. Osteoporotic persons fracture under scenarios of minimal or no loading due to the fragility of bone itself. Fragility fractures are characteristic of fractures occurring under the loading of normal activities (for example, standing, coughing, rolling over in bed) or with falls from a standing height. To the best of our data-mining capabilities, there is no evidence for increased risk of fragility fractures in long-duration crewmembers, nor is there a diagnosis of osteoporosis in these crewmembers by clinically accepted guidelines. However, the current T-score based criteria for risk assessment,

originally developed for older women, are probably not sufficient for assessing risk in a low number of astronauts who are predominantly young, healthy males exposed to skeletal assault that is unlike age-related bone loss.

Parameters of bone micro- and macrostructure contribute to the strength of bone and can be quantified by non-invasive technologies. Uncertainty related to spaceflight effects on bone morphology and on bone strength exist because technologies, including QCT scanning and FEA, to assess such changes have currently been assessed only on a low number of volunteers. Changes to the human skeleton when exposed to a microgravity or fractional gravity environment remain unknown. Low subject numbers and delayed accumulation of data are large constraints to assessing fracture probability for decision-making and mission planning.

With an increased understanding of spaceflight effects and improved measurement capabilities beyond DXA aBMD, we may be able to provide a better assessment of fracture risk to future crew. Additional data could include the temporal pattern of bone loss for missions greater than 6 months and the morphological changes that accompany skeletal adaptation to space, including both microgravity and partial gravity environments. Documented reductions in bone mass and structural changes suggest declines in whole bone strength such that a deconditioned person with bone atrophy is susceptible to fracture at loads that may have been tolerable before spaceflight. A multifactorial analysis of cross-disciplinary risk factors for fracture is also warranted. Finally, modeling the Factor of Risk for fracture during a spaceflight mission requires a full understanding of the changes in bone mass and in bone quality at specific sites as well as how these sites will be mechanically loaded by activities during a spaceflight mission.

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XII. List of Acronyms

aBMD: areal bone mineral density
BFxRM: Bone Fracture Risk Model
BMD: Bone mineral density
DXA: dual-energy X-ray absorptiometry
EVA: Extravehicular activity
HRP: Human Research Program
IMM: Integrated Medical Model
iRED: interim resistive exercise device
ISS: International Space Station
MRI: magnetic resonance imaging
PRA: probabilistic risk assessment
QCT: quantitative computed tomography
vBMD: volumetric bone mineral density