HRP-47065

Human Research Program Integrated Research Plan

Human Research Program

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Revision K

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National Aeronautics and Space Administration
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Human Research Program
Integrated Research Plan

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DOCUMENT CHANGE/ REVISION LOG

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Change/ Revision	Date	Description of Change	Pages Affected
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Revision I, PCN-2	3/27/2018	Revision I, Page Change Notice-2, approved by HRPCB per SA-00678	Appendix A, HRR Content
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1 INTRODUCTION

Crew health and performance are critical to successful human exploration beyond low Earth orbit (LEO). The Human Research Program (HRP) is essential to enabling extended periods of space exploration through research and technology development (R&TD) activities that are aimed to mitigate risks to human health and performance. Human spaceflight risks include physiological and performance effects from hazards such as radiation, altered gravity, and hostile environments, as well as unique challenges in medical support, human factors, and behavioral health support. The HRP delivers human health and performance countermeasures, knowledge, technologies and tools to enable safe, reliable, and productive human space exploration. Without HRP results, National Aeronautics and Space Administration (NASA) will face unknown and unacceptable risks for mission success and post-mission crew health.

1.1 Purpose

The Integrated Research Plan (IRP) describes HRP's approach and R&TD activities intended to address the needs of human space exploration. As new knowledge is gained, the required approach to R&TD may change.

The IRP serves the following purposes for the HRP:

- provides a means to ensure that the most significant risks to human space explorers are being adequately mitigated and/or addressed;
- shows the relationship of R&TD activities to expected deliverables;
- shows the interrelationships among R&TD activities that may interact to produce deliverables that affect multiple HRP Elements, Portfolios, Projects or research disciplines;
- accommodates the uncertain outcomes of R&TD activities by including milestones that lead to potential follow-on activities;
- shows the assignments of responsibility within the program organization and, as practical, the proposed acquisition strategy;
- shows the intended use of research platforms such as the International Space Station (ISS), NASA Space Radiation Laboratory (NSRL), and various spaceflight analog environments including the Human Exploration Research Analog (HERA);
- shows the budgeted and unbudgeted R&TD activities of the HRP, but does not show <u>all</u> budgeted activities, as some of these are enabling functions, such as management, facilities, and infrastructure, and others are internal/discretionary tasks.

1.2 Scope

The IRP documents the tasks necessary to fill the gaps associated with each risk listed and details where (e.g., the ISS or a ground analog) and who (e.g., investigators within a specific HRP organization) will accomplish the task and what is being produced (e.g., risk uncertainty reduction, candidate health or performance standard, or countermeasure strategy). The IRP includes research that can be conducted with the resources available to the HRP, as well as research that would be performed if additional resources were available. The timescale of human

space exploration is envisioned to take many decades. The IRP attempts to describe a plan of research looking forward many years into the future and illustrates the Program's research plan from early beyond Earth orbit (BEO) missions through exploration missions of extended duration. The fidelity of the IRP is quite high in the near term (2018-2022), but decreases with time. The IRP will be regularly revised and updated based on exploration mission development, achievement of key milestones, and consideration of new evidence gained.

The IRP was originally baselined as HRP-47065, Human Research Program Integrated Research Plan, in 2008. In 2010, the detailed technical content (formerly Appendix A) transitioned to the Human Research Roadmap (HRR): http://humanresearchroadmap.nasa.gov/.

1.3 Responsibility and Change Authority

This document, as well as the accompanying HRR, is under Configuration Management control of the Human Research Program Control Board (HRPCB). Changes to this document will result in the issuance of change pages or a full re-issue of the document.

2 DOCUMENTS

The relationship of the HRP documents in Section 2 with the IRP is illustrated in Figure 1. A more detailed explanation of the flow depicted in Figure 1 is provided in Section 3.

2.1 Applicable Documents

The following documents of the specified revision or the latest revision if not identified, are applicable to the extent specified herein.

Document Number	Document Title
HRP-47052	Human Research Program Requirements Document (PRD)
HRP-47069	Human Research Program Unique Processes, Criteria, and Guidelines (UPCG)
Various	Evidence Reports

2.2 Reference Documents

The following documents contain supplemental information to guide the user in the application of this document. These reference documents may or may not be specifically cited within the text of the document.

Document Number	Document Title
HRP-47051	Human Research Program Plan
HRP-47053	Human Research Program Science Management Plan
NASA-STD-3001,Vol. 1 and Vol. 2	Space Flight Human-System Standards, Volume 1 Crew Health and Volume 2 Human Factors, Habitability and Environmental Health
NASA/SP-2010-3407	Human Integration Design Handbook (HIDH)

2.3 Order of Precedence

All specifications, standards, exhibits, drawings or other documents that are invoked as "applicable" in this specification are incorporated as cited. All documents that are referred to within an applicable document are considered to be for guidance and information only.

In the event of a conflict between the text of this specification and an applicable document cited herein, the text of this document takes precedence.

Figure 1. HRP Requirements and Content Alignment

3 CONTEXT OF THE IRP

3.1 Risk Research Portfolio

The Human Systems risks fall within the purview of the Office of the Chief Health and Medical Officer (OCHMO). The OCHMO established the Human Systems Risk Board (HSRB), chaired by the JSC Human System Risk Manager, to ensure a consistent, integrated process for managing human system risks that are critical to successful human exploration beyond LEO. Risks in the HRP research portfolio shall be identified by the HSRB as risks requiring research and documented as requirements in the HRP-47052, Human Research Program Requirements Document.

3.2 Program Requirements

HRP-47052 defines, documents, and allocates the requirements to each of the HRP Program Elements: Exploration Medical Capability (ExMC), Human Factors and Behavioral Performance (HFBP), Human Health Countermeasures (HHC), Research Operations and Integration (ROI) (as an implementing Element, no risks assigned), and Space Radiation (SR). These HRP requirements are derived to satisfy the exploration mission requirements from Human Exploration and Operations Mission Directorate (HEOMD) and the OCHMO as found in NASA-STD-3001, Space Flight Human-System Standards, Volume 1 Crew Health and Volume 2 Human Factors, Habitability and Environmental Health. In addition, NASA/SP-2010-3407, Human Integration Design Handbook (HIDH), was published as a compendium of human space flight history, lessons learned, and design information for a wide variety of disciplines to serve as a companion document to NASA-STD-3001, Volume 2. The HRP has two main responsibilities regarding these standards. In some cases, a NASA-STD-3001 requirement is written in generic terms to ensure its applicability to a wide range of mission environments (such as microgravity in orbit, lunar surface habitation, or transit to Mars). HRP research can serve to inform the standard, refine the requirement, and help define processes or methods (cutting edge or state of the art) to meet the requirement. Where emerging evidence or knowledge may indicate that the standards are not written in a way that captures a complete set of relevant considerations, additional research may be conducted to facilitate an update.

The requirements in the Program Requirements Document (PRD) are divided into three categories: requirements related to human system standards, requirements related to human health and performance risks, and requirements related to provision of enabling capabilities. Each Element, with the exception of ROI, incorporates its respective PRD requirements into its specific Element Management Plan. These Elements subsequently derive a research plan to address the requirements. ROI implements the requirements identified by the other HRP Elements for research and technology demonstration tasks that require the use of the ISS or ground analogs, as appropriate.

3.3 Human Research Program Architecture

The development of HRP content has been formulated around the architecture of:

3.3.1 Evidence

Reviews of the accumulated evidence from medical records, spaceflight operations and research findings are compiled into HRP Evidence Reports. These findings provide the basis for identifying the highest priority human risks in space exploration and are a record of the state of knowledge for each risk in the PRD. The Evidence Reports are available to the scientific community and general public at the following link: http://humanresearchroadmap.nasa.gov/evidence/. The Evidence Reports receive outside independent review and are updated as needed. If new evidence indicates that a risk should be retired or that a new risk should be added, the HRP will, after thorough review with the HSRB, take the appropriate action to modify the PRD and update the Evidence Reports accordingly.

3.3.2 Risks

The HSRB, chaired by the JSC Human System Risk Manager, identifies risks relevant to the Chief Health and Medical Officer (CHMO) and to the health and human performance aspects of the exploration program based on current evidence. Each risk is assigned a risk rating by the HSRB which is used as a tool to communicate to Agency management the seriousness of a risk to crew health and performance when applied to the mission architecture and/or mission characteristics defined for each Design Reference Mission (DRM). The risk ratings are maintained by the HSRB and serve as one of several inputs to determine the priority of each human risk, helping HRP Management make program decisions and allocate program resources. The HRP uses the HSRB forum to communicate updates to the risks resulting from HRP R&TD activities. The HRP utilizes the HSRB to identify risks requiring research. The PRD allocates these risks as requirements to quantify, mitigate, or monitor these human system risks to the appropriate Element within the HRP. The PRD, however, does not establish priority for the risks.

The HRP uses the IRP to describe the approach and R&TD activities intended to address the needs of human space exploration. The risks-gaps-tasks-deliverables detail in the IRP is required to ensure completeness in addressing the risks. The forecasted schedule to mitigate risks is then captured in a chart called the Path to Risk Reduction (PRR). This timeline depicts significant risk milestones associated with improvements in risk ratings.

3.3.3 Gaps

For each risk requiring research, HRP identifies gaps in knowledge about the risk and the ability to mitigate the risk. The degree of uncertainty in understanding the likelihood, consequence and/or timeframe of a particular risk as well as its criticality to the mission(s) are the major factors that drive the priority of the research gaps listed in the IRP. Gaps should represent the

critical questions that need to be answered in order to significantly reduce the risk. Gaps could change over time based on research progress, current evidence, and mission planning scenarios. In some cases, a gap can address multiple risks.

3.3.4 Tasks

The IRP defines the tasks that will provide the deliverables required to fill the gaps. The HRP Elements identify specific research tasks that are targeted at better characterizing a risk or developing mitigation capabilities to reduce the risk to an acceptable level. A major criterion for selection of a specific task is how well the proposed research provides deliverables toward closure of the gap. A task can range from activities that define research requirements or operational needs, such as data mining and literature reviews, to a three to four year grant project selected from proposals that have been submitted in response to the annual HRP NASA Research Announcement (NRA). Even though not specifically a R&TD activity, a data mining task can provide results which are pivotal in defining further steps in the research path, and a hardware evaluation can further the engineering approach to risk mitigation.

Tasks are solicited through an NRA, the Small Business Innovation Research (SBIR) program, NASA Request for Proposals (RFP), etc., or are directed by HRP scientists. The HRP's intent is that most studies are procured through competitive means, i.e., NRA, RFP, etc. In some cases, due to timeliness of data, or close interconnectedness with operations or other NASA entities, the HRP will direct that a specific study be done. Criteria for these decisions are given in HRP-47069, Human Research Program Unique Processes, Criteria, and Guidelines. The current or planned procurement method for each task in this research plan is identified. Identification of any investigation as a directed study within the IRP does not signify a commitment on the part of the HRP to implement that study as a directed study without further consideration by the Chief Scientist as specified in HRP-47069.

It is the HRP's policy that all investigations sponsored by the program will undergo independent scientific merit review. This includes proposals submitted in response to NRAs, all directed study proposals, and all unsolicited proposals.

3.3.5 Deliverables

Each task or progression of tasks is designed to ultimately culminate in deliverables or products that range from risk characterization to prototype technology or countermeasures. Customers for the products delivered by HRP include: the NASA OCHMO; the Medical Operations community charged with astronaut health care; the Astronaut Office; Flight Control Teams working in the Mission Control Center; and the various Programs (International Space Station, Orion, Space Launch System, Advanced Exploration Systems, and Gateway) involved in definition and development of space exploration missions beyond low Earth orbit.

Deliverables provided to external customers are usually the result of the integration and synthesis of evidence and deliverables from a line or lines of research. These deliverables are linked to tasks with Maturation listed as the solicitation mechanism in the HRR. Common deliverables include risk characterization, recommendations for new or updated standards (e.g., Permissible Exposure Limits), requirements (e.g., Net Habitable Volume for a spacecraft), countermeasures,

and technology. Specifications for some deliverables are agreed upon with customers of the HRP products.

Common deliverables include recommended standards (e.g., Permissible Exposure Limit [PEL]), requirements (e.g., flight rule), risk characterization, countermeasures, and technologies. After deliverables are provided, the R&TD results are assessed for applicable updates to the evidence base as it impacts risks, gaps and tasks in order to achieve risk reduction goals as laid out in the PRR.

3.4 Research Platforms

The HRP utilizes various research platforms and data sources to address gaps in knowledge. Data mining involves gathering and analyzing data from historical spaceflights via the Lifetime Surveillance of Astronaut Health (LSAH), previous research data in the Life Sciences Data Archive (LSDA), spaceflight operational data (e.g., landing performance and simulator performance data), and other sources to identify possible correlation with physiologic or psychological function, and relevant data from ground studies (NASA-sponsored and otherwise).

The HRP utilizes the ISS and other flight platforms as they become operational to conduct research requiring the unique environment of space. The spaceflight data primarily identify and/or quantify physiological and behavioral changes to the human system occurring in the microgravity environment. The ISS is utilized to validate potential countermeasures, as an analog for long-duration exploration missions, and to gather data to define space normal as given in Section 3.5.

The use of the ISS platform, in several cases, is critical to obtaining the required knowledge to build products supporting longer, more challenging missions. The Shuttle retirement in 2011, the uncertainty in replacement transport vehicles to ISS, and the planned retirement of the ISS in 2024 levy significant constraints on available flight resources. However, since not all research that requires the ISS can be accomplished by 2024, the HRP will continue to plan use of the ISS as a viable research platform should the vehicle retirement be extended beyond the 2024 timeframe or an alternate LEO or analog platform can be found. Where possible, the HRP will utilize ground-based analog environments to perform the research required to fill gaps in knowledge, preserving the limited flight resources for only those that cannot be addressed elsewhere. HRP utilization of the ISS is managed by the ROI Element.

There are several analog environments utilized by the HRP, some owned and operated by HRP, some by NASA, and others operated by other agencies. Each analog environment is assessed for its characteristics and the fidelity with which relevant portions of the flight environment are represented (e.g., isolation & confinement, extreme environments). No ground-based analog can serve to simulate the flight environment completely; thus each analog selected for use is based on its important flight-like characteristics specific to the task objectives. The use of several analogs may be required to fill a gap. Throughout the IRP, tasks requiring the use of specific analogs are identified. The ROI Element, coordinates utilization of some ground-based research analogs to complement space research. HRP utilization of the NSRL is managed by the SR Element.

3.5 Functional Definition of Space Normal

Space normal is defined for this document as the normal human response to prolonged spaceflight. As NASA prepares to send crewmembers on extended exploration missions, questions arise regarding the impacts of the spacecraft and surface exploration environment on the health, safety, and performance of the explorers. The normal human response to prolonged microgravity exposure during (and after) orbital spaceflight missions has received considerable research attention, but little is known about the human physiological responses to prolonged fractional gravity exposure. It would be useful to know ahead of time whether any of the effects could be severe enough to cause functionally significant decrements in crew health, safety, or performance during these missions, so that appropriate countermeasures could be provided from the outset.

All organ systems are affected by the environmental factors associated with spaceflight, although the time frame and degree of negative impact on astronaut health and performance is highly variable. The spectrum of consequences to human health and performance ranges from catastrophic through steady loss or decrement, to short-term transitional adjustment, to benign with no meaningful impact. Currently, the HRP approach for each physiological condition or organ system of concern is to:

1. document the acclimated state;
2. recommend revisions to crew health standards if that state is medically unacceptable;
3. if unacceptable, then determine physiological mechanisms of action; and
4. develop countermeasures as appropriate.

The acclimated state is understood to represent space normal, the newly adapted normal baseline physiological state. A rigorous definition of space normal must consider the presence or absence of pre-existing clinical conditions and legacy countermeasures, as well as variability in incident SR, ambient atmospheric pressure, temperature and composition; acoustics; lighting; etc., in addition to the absence of apparent gravity. In particular, all experiments currently defining space normal on ISS are conducted in the presence of an exercise prescription that has varied from mission to mission and astronaut to astronaut over the first decade of ISS operations.

With an accepted definition of space normal, HRP would be in a position to recommend whether or not to allow acclimation to spaceflight conditions, and if so, to what degree: acclimation followed by treatment just prior to or after Earth return; acclimation accompanied by in-flight monitoring and countermeasures implementation at a predetermined degree of decrement; or no acclimation permitted whatsoever.

3.6 Hardware and Countermeasure Development Cycles

Many HRP deliverables contribute to hardware development. NASA hardware development proceeds through several stages, with reviews occurring between the stages. The exploration program goes through these stages as it designs the next crew capsule, a lunar lander, and the next generation space suit. Common reviews seen in the HRP documentation are as follows:

- System Requirements Review (SRR): At the beginning of the project, establishes what the system will and will not do.
- Preliminary Design Review (PDR): At 10% design completion, is primarily to critique the architecture of the design and critical decisions made in the design.
- Critical Design Review (CDR): At 90% design completion, is primarily to make a last set of changes before the design is finalized.

To make sure that all the organizations within NASA and its associated contractors are working from the same set of plans, NASA uses a rigorous "configuration management" system to obtain, review and implement changes to key documents. A change is initiated by a formal document called a Change Request (CR). A CR often solicits input from many stakeholders. That input is often provided in the form of a Review Item Discrepancy (RID). A RID is essentially a request to change part of a document and includes the rationale. The owner of the document decides whether or not to make the change. The HRP often provides RIDs to CRs concerning exploration program documents. This is the NASA process that allows HRP results to change NASA's plans for exploration vehicles.

Design solutions and technology typically must be defined to a Technology Readiness Level (TRL) 6 by the PDR. TRLs are defined in Appendix B.

The HRP nominally begins a countermeasure development at Countermeasure Readiness Level-4 (CRL-4) and develops the selected countermeasure to CRL-7 or -8. At this point, the HRP transfers the countermeasure to the implementing organization for incorporation. For some Elements, SR for example, countermeasure development must begin at much lower CRLs and are thus developed to CRL-6 prior to transition. CRLs are defined in Appendix B.

4 RESEARCH APPROACH

The IRP describes a plan of research that addresses both human physiology, human performance and the interconnected system of the human and spacecraft in a highly integrated manner. It is often not possible to address the risks simply as stand-alone units. The knowledge or mitigation gaps often appear in multiple risks. Many of the specific research tasks address multiple gaps across risks.

In the following sections, the PRD risks are listed by HRP Element. Sections 4.1 through 4.4 provide a high-level view of the research approach to the risks. More detailed research findings, including citations, can be found in each risk's Evidence Report on the HRR. The HRP Elements are arranged in the following order:

1. Exploration Medical Capability
2. Human Factors and Behavioral Performance
3. Human Health Countermeasures
4. Space Radiation

Detailed information about gaps and tasks for each risk is located in the HRR: http://humanresearchroadmap.nasa.gov/.

The interactions between the risks, gaps, and tasks are not readily shown in a printed book. In the HRR database, the user will be able to search for such items as gaps associated with a risk, the tasks associated with a given gap, the cross-integration of a task across multiple gaps or risks, and deliverables associated with a gap or task.

4.1 Exploration Medical Capability

4.1.1 Risk of Adverse Health Outcomes & Decrements in Performance due to Inflight Medical Conditions (Short Title: Medical)

A human mission to Mars is a challenge outside of the bounds of human experience, but within the grasp of our technology and imagination. It is critical to both draw lessons from prior spaceflight experience and to recognize the limits of that experience. Relying too heavily on prior spaceflight experience creates a risk of not challenging assumptions inapplicable to planetary exploration. Each medical system designed for earlier human spaceflight was developed for a close-proximity Earth-centered mission that enjoyed the advantages of real-time telemedical support, consumable resupply, and medical evacuation when necessary. Operating outside low Earth orbit, without these advantages, requires a closer alignment between vehicle engineering and medical system development.

In a real sense, success in a human Mars mission will depend on a comprehensive and mission-enabling astronaut healthcare system as well as an understanding of how such a system will be integrated and implemented within an exploration mission. All other design, requirements, and research within exploration medicine will be driven by these two goals; thus, these goals form the conceptual cornerstone that defines the medical system design and the supporting research pathway. Using this framework, the ExMC Element works to envision the medical needs for a human Mars mission, identify operational barriers to meeting those needs, and implement a research pathway in the support of agency requirements and stakeholder interests.

The medical challenges expected in a human Mars mission are unlike any prior manned spaceflight experience. As a result, provision of medical care within the limitations of such a mission requires a paradigm shift in the understanding and acceptance of risk, the ethical framework of experimental flight, and the trading of medical capabilities against other vehicle components within a vehicle architecture limited by mass, volume, power, telemetry, and many other factors unique to distant and interplanetary travel. Human spaceflight has reached a critical moment where the transition to a human-centric mission architecture must become reality if exploration missions are to succeed. Medical system requirements and vehicle design must share dependence to minimize the risks to crews, and flexible and minimized technologies must factor heavily in system design to elevate a medical capability without sacrificing other systems components designed to keep our crews safe. It is imperative that the medical system balance these constraints to ensure that crew health and performance is maintained and mission risks are minimized.

The ExMC Element is specifically concerned with establishing evidenced-based methods of monitoring and maintaining astronaut health. Essential to completing this task is the advancement in techniques that identify, prevent, and treat any health threats that may occur during space missions. These techniques, in turn, must be supported by an evidence-based medical data handling system appropriate for long-duration, exploration-class missions. The ultimate goal of the ExMC Element is to develop and demonstrate a pathway for medical system integration into vehicle and mission design to mitigate the risk of medical issues.

ExMC is applying systems engineering principles and practices to accomplish its integrative goals. The systems engineering activities apply a structured and disciplined technical approach to support development of a medical system addressing clinical, behavioral health, human factors, physiological performance, and task performance needs. The systems engineering activities also enable effective coordination and integration with exploration mission engineering, operational, and technology development efforts by communicating with products (e.g., requirements, interface descriptions) typically used in those communities. Tools to support the evaluations and trades among quantitative risk metrics, clinical capabilities, technical requirements, and system implementation options, and tools that address changing risk throughout a mission will be necessary. Because of the novel nature of the risks involved in exploration missions, new and complex ethical challenges are likely to be encountered.

4.1.2 Risk of Renal Stone Formation (Short Title: Renal)

Historical spaceflight data have revealed multiple in-flight and post-flight instances of renal stones. While none have led to loss of crew life, there have been in flight medical conditions leading to either evacuation or early termination of mission. Renal stone formation in microgravity has been well studied and modeled. Recent results from first principles simulations starting with the chemistry of renal stone formation and ending with associated risk have provided validated models quantifying the risk of clinically significant renal stones during exploration as a function of hydration, nutritional countermeasures, and gravitational environment. Current research efforts are aimed at 1) in-flight strategies to reduce stone formation, 2) ultrasound diagnostics for early detection of stones, and 3) operational interventions, such as moving renal stones through the application of ultrasound waves.

4.1.3 Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight (Short Title: Stability)

NASA's current Low Earth Orbit (LEO) operations involve frequent resupply missions that may be problematic for some long duration missions and impossible for Deep Space and/or Planetary missions. As such, ensuring a safe and effective pharmacy for exploration missions is an important future challenge. At this time, it is unclear how, and to what extent, 1) the spaceflight environment changes drug stability and 2) alterations of human physiology affect drug pharmacokinetic and pharmacodynamic properties. The potential for drug instability compounded by altered drug response poses a significant risk to exploration crews. Current research efforts are underway to propose a safe and effective exploration spaceflight formulary able to maintain a ≥ 3 year shelf-life. The proposed ExMC research includes studies that will provide validation for chemical / physical pharmaceutical stability, degradation product toxicity,

drug safety profiles, and better characterize pharmacokinetics, pharmacodynamics, and pharmacotherapeutic properties of medications in spaceflight.

4.1.4 Risk of Adverse Health & Performance Effects of Celestial Dust Exposure (Short Title: Dust)

The impact of exposure to dust from extraterrestrial sources (celestial dusts) could lead to serious respiratory, cardiopulmonary, ocular, central nervous system (CNS), or dermal harm during exploration-class missions, resulting in immediate or long-term health effects. NASA needs to understand the implications of exposure to these dusts so vehicle and habitat designs will include features that maintain concentrations of airborne dust within safe limits and operations minimize the risk of abrasion to the skin and eyes. NASA rodent based research results coupled with expert review have established a permissible exposure limit for lunar dust that has been converted into a NASA standard. Current research focuses on refining and creating new standards for other celestial body dust exposures based upon dust composition and surface operations.

4.1.5 Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (Short Title: Fracture)

Spaceflight-induced bone atrophy is largely targeted to specific regions of the skeleton that experience larger deficits in mechanical loading in microgravity. These areas are more at risk for fracture during exploration missions. The risk for fracture is minimal during missions in microgravity because applied loads associated with falling, or with crushing, are essentially non-existent. Mechanical loads to bone, however, will increase in the gravitational environment of celestial bodies and 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. Computational modeling performed in support of the Integrated Medical Model, however, suggests that mechanical loads imparted to bone during a fall on the Moon or Mars are unlikely to be hazardous. There is no active research regarding bone fracture at this time as the risk is considered “accepted” for all Design Reference Missions.

4.2 Human Factors and Behavioral Performance

4.2.1 Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (Short Title: BMed)

HFBP research addresses the risk of adverse cognitive and behavioral conditions and psychiatric disorders developing during or following a spaceflight mission. Early detection and mitigation of stress or other risk factors during spaceflight is imperative to deter development of behavioral or psychiatric conditions which could seriously harm and negatively impact the individual or the crew, and pose serious consequences for accomplishing mission objectives or jeopardizing these mission altogether. For long-duration space exploration, early detection and delivery of countermeasures to crew with increased autonomy, reduced communication capabilities, and

limited resupply is essential to the health of spaceflight crewmembers. Toward this end, HFBP is developing methods for monitoring behavioral health during a long duration exploration mission, and adapting/refining various tools and technologies for use in the spaceflight environment. These measures and tools will be used to monitor, detect and treat early risk factors that contribute to adverse cognitive and behavioral conditions, as well as psychiatric disorders. HFBP will utilize analogs and, where appropriate, spaceflight, to test, further refine, and validate these measures and tools for future missions. HFBP also develops countermeasures for maintaining behavioral health and enhancing performance during long duration isolated, confined, and highly autonomous missions; provides recommendations for spaceflight medical operations; and, provides updates for human health and performance standards, and habitability and human factors standards.

The magnitude of physical and biological stressors will vary by mission phases but will simultaneously, perhaps synergistically, and cumulatively act on the human system with the potential to adversely impact operationally-relevant crew performance. Three high priority risk factors -- space radiation, isolation, and altered gravity exposure—may synergistically impact the CNS (Central Nervous System), and subsequently, crew cognitive and behavioral health and performance, on long-duration missions. To that end, HFBP leads the development of a fully integrated research approach referred to as the CNS/BMed/Sensorimotor (CBS) Integrated Research Plan, which brings together needed research across three risks:

- Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure, (CNS); the integration focuses on the Acute phase of the CNS risk
- Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (BMed)
- Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Spaceflight (SM)

Complementing behavioral performance measures, the CBS Integrated Research Plan identifies a need to assess brain physiology, neurovascular unit integrity, molecular signaling, and biomarker changes, in order to generate data sets that can be incorporated into computational models to represent and predict changes in operationally-relevant “brain performance pathways”.

The CBS Integrated Research Plan integrates scientific expertise within the 3 discipline areas (space radiation, sensorimotor and behavioral health) to operationalize a risk-assessment approach to define crew health and performance related to: Operational performance and fitness for duty standards relative to each risk within the framework of Performance Outcome Levels (POL), and Radiation Permissible Exposure Limits (PEL) (established by assessing the relative risks of the three CBS Integrated Risks). The plan aims to deliver standards and guidelines development (including POLs and PELs). This requires complementary, translational approaches to identify the mechanisms, pathways, and components that contribute to operational performance risks by:

- Appreciation of multifactorial nature of spaceflight hazards, exposures, & dose-effect responses (i.e., differential variability due to differences in vulnerability to hazards).
- Consistent/valid animal translational models (and back-translational approaches), along with human biomarkers and measures to assess the function of some mechanisms

discovered in animal models, used to develop a multidimensional set of validity criteria that is then generalized to relevant human risk.

- Leveraging translational and computational modeling to integrate traditional and novel data (e.g., animal model analogues of brain-behavior risk translated to human performance).
- Strategic leveraging of transdisciplinary expertise in more transparent approach focused on integration of approaches, data and technology to attain greater confidence in risk assessments.

4.2.2 Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (Short Title: CNS)

A critical question for the current phase of research is to establish possible threshold doses for specific central nervous risks (CNS) risks. CNS risks from galactic cosmic rays (GCR) are a concern due to the possibility of single high charge and energy (HZE) nuclei traversals causing tissue damage as evidenced by the light-flash phenomenon first observed during the Apollo missions. Also, as survival prognosis for patients irradiated for brain tumor treatment has improved, patients have shown persistent CNS changes at times long after treatment with gamma rays suggesting a possible CNS risk for a large solar particle event (SPE). Furthermore, animal studies of behavior and performance with HZE radiation suggest detrimental changes may occur during long-term GCR exposures. Currently, there is no projection model for CNS risks of concern to NASA. The values of possible thresholds for CNS risks and knowledge on how to extrapolate possible thresholds to individual astronauts is a key milestone in the long-term research plan. HFBP is working with HHC and SR in support of the Integrated CBS plan (see section 4.2.1).

4.2.3 Risk of Performance and Behavioral Health Decrements Due to Inadequate Cooperation, Coordination, Communication, and Psychosocial Adaptation within a Team (Short Title: Team)

This risk focuses on developing and maintaining high-performing and well-functioning spaceflight teams, including both flight crew and ground support. While relatively few empirical spaceflight studies have been conducted regarding the impact of interpersonal and intrapersonal factors on performance, a growing body of evidence from spaceflight-like environments suggests that team-level issues could jeopardize long-duration exploration missions. Reports from Mir reveal that several missions may have been terminated earlier than planned due to friction between crewmembers, and some veteran NASA astronauts have reported conflict during previous space travels. Understanding the potentially negative impacts of inter- and intra-personal issues from both spaceflight and high-fidelity analog environments is important for identifying countermeasures to aid flight and ground crewmembers during future high-autonomy missions (e.g., cislunar space and Mars).

A series of HFBP-funded literature reviews and interviews of crew and operations personnel identified the most likely and most serious threats to crew cohesion, crew performance, and crew-ground interaction that might be expected for long-duration exploration missions. Follow-on studies are currently collecting data in high-fidelity analogs such as NASA's HERA with the

goals of identifying the critical drivers of team and multiteam systems functioning; validating objective measures for monitoring crew cohesion and processes, composing teams with the right mix of characteristics, coordinating under communication delays, and variable autonomy due to shifting mission requirements; and developing approaches to enhance team training related to teamwork skills and multi-cultural crews. Deliverables will build upon the current highly successful in-flight support services and countermeasures to mitigate risks associated with increased isolation, confinement, duration, and communication delays. These measures and countermeasures are assessed for feasibility and acceptability in appropriate analog environments, to include inflight studies examining the cohesion and performance of ISS crews.

4.2.4 Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload (Short Title: Sleep)

Objective and subjective evidence indicates that during ISS and Shuttle missions, sleep is reduced and circadian rhythms are misaligned. As measured by actigraphy and accompanying sleep logs, the average nightly sleep duration of crewmembers for both short and long duration missions is around six hours, with astronauts showing a significant increase in sleep duration once they return to Earth, indicating a sleep debt may have accrued on orbit.

Ground evidence demonstrates that performance impairments can occur when sleep is attained in quantities similar to that attained by astronauts in flight. In addition, preliminary results from a flight study on the ISS demonstrates that reaction time is impaired as a function of reduced sleep. Future spaceflight data mining efforts may also yield insight into the relationship between sleep duration and circadian phase, with other outcomes (e.g., immune health, operational performance).

HFBP research aims to further characterize and quantify this risk by implementing studies on ISS using standardized measures to evaluate performance relative to fatigue and performance. Planned data mining efforts seek to further investigate contributors to sleep loss, fatigue, circadian desynchronization, and work overload by evaluating environmental factors, individual vulnerabilities, and mission timelines relative to sleep. The role of sleep and circadian phase in other outcomes (i.e., BMed and Team studies) will also be further evaluated through analog research.

Such investigations help to inform the optimal countermeasure strategy for mitigating the health and performance effects of sleep loss and related issues in flight. As an example, studies indicate that properly timed light exposure can help maintain circadian alignment, and/or facilitate schedule shifting, performance and alertness. Current efforts aim to determine the operational protocols and technical requirements for lighting systems on the ISS, as well as future exploration vehicles. Other countermeasures that are currently being investigated include sleep-wake models of performance that may inform real time scheduling decisions as well as optimal ways to individualize countermeasure regimens. The effectiveness of other potentially relevant countermeasure strategies, such as stress management, diet, and exercise, may also be assessed.

4.2.5 Risk of an Incompatible Vehicle/Habitat Design (Short Title: Hab)

This risk focuses on enabling the provision of living and working environments that were designed specifically to accommodate its human users, thus reducing negative impacts to task performance and behavioral health caused by incompatible vehicle/habitat design. This risk applies to any habitat designed for travel or operation outside Earth's atmosphere wherein crew must work and live, including launch and transfer vehicles, pressurized suits or other occupied and confined space (e.g., space station, non-Earth outpost, re-entry capsule, rovers). Examples of short-term effects include overexertion, difficulty in reading a checklist due to spacecraft vibrations or inadequate lighting, high temperatures in a module due to inefficient co-location of habitability-related hardware and excessive activities, difficulty donning a suit due to inadequate habitable volume, or difficulties communicating with fellow crewmembers due to high levels of noise in the cabin. Performance-related inefficiencies may include unnecessary translations between workstations to complete tasks, and increased task completion time due to difficulty in accessing equipment. Examples of the long-term effects include ergonomic injuries or cumulative trauma disorders that are a result of repetitive motions, sustained maintenance of awkward postures, inadequate workspace clearances resulting in frequent over-exertions, suit hardware requiring sustained performance at excessively high sub-maximal levels, and permanent hearing loss. Additionally, poor habitat design in conjunction with long-duration isolation may lead to the decreased quality of crew behavioral health (see also Risk of Adverse Behavioral Conditions and Psychiatric Disorders) and impact team performance (see also Risk of Performance and Behavioral Health Decrements Due to Inadequate Cooperation, Coordination, Communication, and Psychosocial Adaptation within a Team). Strategies to address this Risk are focused on the development of tools and processes provided to designers for layout and use of volume; the development of tools and processes that NASA programs or projects can use to better assess habitability impacts of designs; and updates to standards that drive vehicle and habitat designs based on research findings.

4.2.6 Risk of Inadequate Design of Human and Automation/Robotic Integration (Short Title: HARI)

This risk focuses on the appropriate integration of humans with highly autonomous and complex space systems, which includes robotic systems as well as space vehicles. NASA's future missions will involve more extensive, autonomous interaction between humans and automated and robotic systems to accomplish mission goals in near- and deep-space exploration and during surface operations on near-Earth-objects and planetary surfaces. Human-robot teaming will extend to a variety of classes of robotic systems (including dexterous, heavy-lift and mobility systems). Robotic systems and their human interfaces must be designed to support all levels of human operation (e.g., direct manual control, teleoperation shared control, and supervisory control), while also supporting multiple robot operators in multi-agent team configurations, with those operators separated by time, space, or both. Automation will be an integral part of both ground and flight systems as crews work more independently of ground support teams and use robotic systems to achieve mission objectives. The complexity and level of interaction between the flight crew, ground crew, robotic, and automated systems relative to today is expected to change. Systems must be designed to support multiple operators, varying communication delays between flight and ground crew, and increasing reliance on automation. Similarly, the integration of automation systems with their human users requires supporting a variety of role divisions: the

allocations of authority and autonomy between human and automation—with dynamic changes that depend on task or context. Research will focus on identifying the appropriate design for integration of crew with automation/robotic agents to reduce the risk of crew injuries, crew inefficiencies, and failed mission objectives.

4.2.7 Risk of Inadequate Human-Computer Interaction (Short Title: HCI)

This risk focuses on human-computer interaction (HCI), which encompasses all the methods by which humans and computer-based systems communicate, share information, and accomplish tasks. When HCI is poorly designed, crews have difficulty entering, navigating, accessing, and understanding information. Future exploration missions pose a new challenge for HCI in space operations. Unlike missions of the past, crews may experience time delays and communication blackouts that limit their contact with Mission Control. This increased autonomy will force them to rely heavily or exclusively on the information systems available to them within the vehicle or habitat. If displays are not designed with a fully developed operations concept, fine-grained task analysis, and knowledge of human information processing capabilities and limitations, the format, mode, and layout of the information may not support task performance. If interfaces to onboard intelligent systems (required for crew to operate autonomously) are not designed to promote ease of use and trust, the result may be increased task execution errors, which endanger mission goals, crew safety, and mission success.

4.2.8 Risk of Inadequate Mission, Process and Task Design (Short Title: MPTASK)

This risk relates to the appropriate design of mission tasks, task flows, schedules, and procedures. It includes the development and validation of methods and tools for mission, process, and task design. The risk includes a key focus upon establishing an effective operational tempo for crewmembers, which is driven by the scheduling and execution of mission tasks. The operational tempo affects workload and situation awareness of crewmembers: low workload levels have been associated with boredom and decreased attention to task, whereas high workload levels have been associated with increased error rates and the narrowing of attention to the possible detriment of tasks. Operational tempo, scheduling and execution of tasks is done in synchrony with ground control personnel, and this interaction must also be considered, particularly as crew autonomy increases.

Effective task execution is also driven by the quality and presentation of procedures. Whether procedures are provided as written directions, checklists, graphic depictions, tables, charts or other guidance, a given task may be executed inefficiently or incorrectly (possibly resulting in risks to health, hardware, or the mission) if the concept of operations or the procedures are not designed to accommodate human capabilities and limitations. Guidelines for designing task flow, schedules, and procedures that accommodate human capabilities and limitations are required. Inadequate task design may result in increased workload, crew inefficiencies, and failed mission objectives for long duration missions.

Situation awareness (SA) is also a key factor in the execution of tasks. SA refers to the perception of environmental elements with respect to time and/or space, the comprehension of their meaning, and the projection of their status after something has changed, such as time. For example, a crewmember may be monitoring parameters on multiple displays. He/she must be

able to perceive relevant changes in those displays (e.g., component temperature rising), comprehend what that means in context (e.g., component approaching upper temperature threshold/overheating), and be able to predict what may happen next (e.g., failure of the component, potentially leading to a caution message and other outages). During spaceflight, situation awareness must be maintained for a multitude of variables across multiple human interfaces or displays.

The MPTASK risk takes into consideration these and other important task related factors, focusing upon the development and validation of tools for the design, evaluation, and management of missions, the processes by which they are managed, and the tasks used to accomplish them.

4.2.9 Risk of Performance Errors due to Training Deficiencies (Short Title: TRAIN)

NASA's future exploration missions will require astronauts to operate autonomously from the Earth-based Mission Control Center due to distance from earth, communication delays, and possible communication blackouts. Astronauts will need to work together as a team to diagnose and respond to high-risk, critical situations, to command, operate, and maintain their spacecraft, and to conduct scientific research in support of mission objectives. This will require a small, well-trained crew prepared to perform critical tasks and make challenging decisions necessary to achieve mission success, all without access real-time ground support. Inadequate preparation and training could result in errors during mission operations; errors ranging from low to high consequence for the crew and mission.

Historically, spaceflight operations have mitigated potential execution errors in at least two ways: specially-trained crewmembers are assigned to missions or rotated into the operational environment when complex, mission-critical tasks must be performed; and, execution of tasks are closely monitored and supported by ground personnel who have access to far more information and expertise than an individual operator. However, emerging Design Reference Mission architectures include long-duration operations in deep space. Simply increasing the pre-mission ground training time will not address the need for increased training retention, and may even exacerbate the issue. Deep space operations do not allow for assignment of new crew or rotation of crew to ground for training. Further, delays in communication will have a disruptive effect on the ability of Earth-based flight controllers to monitor and support space operations in real time. Performance errors of critical tasks may result in crew inefficiencies, failed mission objectives, and both short and long-term crew injuries. This requires the identification of appropriate methods for Just-In-Time training, and the extent to which materials, procedures, and schedules of training should be modified. Consequently, it is necessary to develop an understanding of how training can be tailored to better support long- duration deep space operations.

The success of future exploration missions depends on effective training that facilitates the acquisition of knowledge and skills, supports the long-term retention of these knowledge and skills, leverages technological innovations, and maximizes the transferability of such knowledge and skills to new situations and new tasks. Without the real-time ground support to mitigate

retention issues and provide real-time expertise, especially for unanticipated, urgent anomalous events, crew pre-mission, onboard, and just-in-time training will be critical to mission success.

Creating such an effective training program to support deep space, exploration missions and reduce the risk of performance errors depends on the application of scientific principles of learning, retention and transfer that are most relevant to space flight operations. Thus, the Training Risk is conducting research to understand these principles and to apply them in the development of the most effective methods and tools for the training of NASA's future crews. This includes research on the level of simulation and simulator fidelity necessary for training mission critical skills, research on the effects of the space flight environment (which includes, but is not limited to space radiation, isolation and confinement, and sleep deprivation) on the retention and transfer of pre-mission training, research on validated, objective measures of training across critical technical domains, and research on the training concept of operations for deep space missions.

4.2.10 Risk of Injury from Dynamic Loads (Short Title: Occupant Protection)

Future spacecraft systems may include launch-abort systems and parachute-assisted, capsule landings. Because of these potential design features, dynamic loads transmitted to the human may result in higher forces than currently experienced during spaceflight. The current standards and requirements do not adequately document the acceptable limits of forces and/or direction of force vectors which can be transmitted to the human without causing injury. Injuries may impair or prevent a crew-member from unassisted evacuation of the spaceflight vehicle after landing. Development of Agency-level human health and performance standards appropriate to occupant protection from dynamic loads, as well as development of the method(s) of meeting those standards in the design, development, and operation of mission systems, would reduce the likelihood of this risk so that crew injury or Loss of Crew (LOC) may be avoided or reduced. In addition, the Columbia Crew Survival Investigation Report cited inadequate upper body restraint and protection as a potential lethal event, and recommended that future spacecraft suits and seat restraints should use state-of-the-art technology in an integrated solution to minimize crew injury and maximize crew survival in off-nominal acceleration environments (L2-4/L3-4), and should incorporate conformal helmets and neck restraint designs similar to those used in professional auto racing (L2-7). Because all crewmembers must endure dynamic phases of flight, detailed understanding of the human body response to such environments is critical. Give that spaceflight deconditioning causes decreases in bone strength, decreases in muscle strength, and increases in bone fracture risk, the criticality of this understanding is greater with longer duration spaceflight missions.

The Occupant Protection Team at NASA has developed a forward plan to develop new standards for protecting the crew during dynamic phases of flight. In collaboration with external peers in industry, academia and other government agencies, the Team will develop and validate the standards using a combination of data mining, testing, analysis, simulation and expert opinion.

4.3 Human Health Countermeasures

4.3.1 Risk of Inadequate Nutrition (Short Title: Nutrition)

Nutrition will be critical to the success of future crewed space exploration missions. During these long-duration, confined missions in the harsh environment of space, nutrition will be an essential countermeasure for maintaining the health of astronauts. Outside of low-Earth orbit, lack of fresh food resupply will further constrain nutritional support of crew health, and increased radiation exposure will increase risks of oxidative stress and resulting tissue damage.

Foods must be palatable, interesting, and chemically stable for the duration of the mission to ensure it meets the nutritional needs of the astronauts. A limited variety of food and repetition of menu cycles could lead to reduced intake and inadequate nutrition. Furthermore, while the nutritional quality of the ISS food system has improved in recent years (e.g., reduced sodium), space food still does not meet many basic nutritional guidelines. For example, the ISS food system is limited in sources of omega-3 fatty acids and has limited selection of fruits and vegetables: food types that have extensive health benefits on Earth. The Food Physiology study is designed to evaluate effects of providing more sources of these beneficial foods and evaluating effects on immune, microbiome, and nutritional outcomes. This is a first, critical element in documenting the benefits of nutrition.

NASA expects Mars missions to take up to 3 years, and vehicles will no doubt have mass and volume limits that will constrain the variety and quality of food. Even on shorter-duration Gateway and Lunar missions, there will be no resupply vehicles to deliver fresh foods to the crew, as on ISS. "Meal Replacement" bars have been developed to help reduce mass and volume but ground testing has revealed that these have negative effects on dietary intake, health, performance, and morale.

The most basic role of food and nutrition is to prevent nutrient deficiency. On Earth, the variety of foods we consume can help stave off frank deficiencies, although the typical western diet is still limited in some nutrients (e.g., vitamin D). Individuals who limit their intake of certain foods or food categories increase their risk of nutrient deficiencies—for example, vegetarians need to be mindful of meeting protein, iron, and vitamin B12 requirements; people who avoid fruits and vegetables are at greater risk of vitamin deficiencies; people who avoid lactose are at risk of calcium and potassium insufficiency, and individuals who are trying to lose weight by reducing calories or following defined diet protocols often have micronutrient deficiencies.

Although nutrition plays a significant role in long-term health and disease states (including cardiovascular disease, cancer, bone loss and osteoporosis, muscle loss and sarcopenia, dementia and cognitive decline), nutrition experts traditionally recommend dietary allowances that are simply designed to prevent deficiencies. That is because we know much less about the effects of diet and nutrition on performance than we do about how to prevent nutrient deficiency. For exploration missions outside of low-Earth orbit, while we must also stave off deficiency, we must understand how food and nutrition interact with the human system to optimize health and performance. This becomes even more critical in space, where environmental factors (e.g., radiation, CO_2), a closed environment, and stress can all affect metabolism, physiology, biochemistry, health and performance. Nutrition can positively (or negatively) affect cardiovascular and ophthalmologic physiology (and pathophysiology), immune system function,

bone and muscle loss, response to exercise and EVA, and more. Dietary intake helps maintain hydration and reduce renal stone risk. Food choices and nutritional status affect mood and improve a crewmember's performance and team cohesion. Optimal nutrition also improves exercise performance, maintains circadian rhythms, and promotes sleep.

Crewmembers must be adequately nourished before, during, and after missions. While preventing nutrient deficits inflight is crucial, optimizing nutrition before will maintain crew health and enable mission success, and proper nutrition will also be important in postflight rehabilitation and return to flight status. Food and nutrition serve as an obvious behavior/performance countermeasure – before, during, and after flight.

An important element of nutritional assessment is to monitor inflight dietary intake. In 2016, a custom iPad App was deployed—the ISS Food Intake Tracker (ISS FIT); this software tracks food consumption and provides the crew with real-time nutrition feedback. In addition to providing information on food use and inventory, ISS FIT helps crewmembers select meals in preparation for specific tasks (EVAs, prep for return to a gravitational field). The response from crewmembers has been outstanding, and highlights the importance of providing tools to both enhance autonomy, and provide greater insight into actual intakes. While we have only scratched the surface so far, we have identified relationships between food intake and changes in nutritional status, as well as relationships between nutrient intake and oxidative stress. A key gap that remains is being able to relate nutrition with other clinical outcomes. This is hindered by the limited insight into these issues, and the lack of interaction between science and operational teams.

Research over the past 10-15 years has yielded many findings. One specific example, the "Nutritional Status Assessment: SMO-016E (Nutrition/SMO-016E)" project yielded numerous insights regarding human nutrition in spaceflight and provided biochemical evidence for inter-individual risk for developing vision and ocular issues during spaceflight, and ultimately documented a genetic predisposition for some astronauts to develop these issues: a finding that the ISS Program Scientist declared the most compelling human research from ISS in 2016. Subsequent studies identified differences in response to carbon dioxide exposure in some individuals based on their genetics. This research highlights the need for individual assessments on the role of genetics on nutritional requirements, which will be required for successful exploration missions and could potentially have profound implications for terrestrial medicine. Countermeasures have been proposed based on this line of research, and these need to be tested.

Another Nutrition Supplemental Medical Objective (SMO) finding was that iron stores increase early in spaceflight and then return to pre-flight concentrations by the end of a six month mission. Increased iron stores during flight were associated with increased oxidative damage to deoxyribonucleic acid (DNA), and also correlated with bone loss. Crewmembers that consumed more iron had a greater iron response during flight (and a greater oxidative damage, and regional bone loss). Given that the ISS food system provides more than 3x the defined iron requirement per day, this is an area where food provisions could clearly help mitigate risks.

Additionally, data from the Nutrition SMO also showed that high levels of urinary calcium resulting from bone loss have clogged the ISS Urine Processor Assembly (UPA) and this

resulted in the recommendation that astronauts increase their fluid intake. The ISS Program used the data to make decisions regarding operational limits for the ISS UPA, providing an estimated savings more than 80 L of water *not launched* every year since 2012.

A follow-on to the Nutrition SMO, the "Space Biochemistry Profile (Biochemical Profile)" provided an updated, broad spectrum of biochemical testing from blood and urine in support of operational and research activities. This effort was stopped in 2018.

While all concede that food will be flown for exploration missions, there is little concession that we need to understand optimal composition of that food. The food system for low Earth orbit mission was initially designed simply to meet cost constraints (i.e., commercially available items). The role for nutrition in terrestrial health is evident. We need to document the extent to which we can mitigate the negative effects of spaceflight on human adaptation and performance.

Food and nutrition are the only countermeasure that we can be absolutely positive will be onboard exploration missions. We have a choice: we can do as some ship captains did centuries ago, denying the reports of the effects of citrus fruit, and argue instead that clean galleys and fresh meat would eradicate scurvy. Or we can use nutrition to optimize crew health during these exploration missions, helping to ensure mission success while imparting long-lasting benefits on crew health.

4.3.2 Risk of Early Onset Osteoporosis Due to Spaceflight (Short Title: Osteo)

The Fracture and Osteo risks are interrelated because they have the same physiological outcome—bone fracture. However, the risks differ regarding the type, cause, and timing of fracture, and the mitigation approach and resources. The descriptions of spaceflight-induced skeletal changes will inform both risks. The crux of managing both risks depends on the ability to estimate when fractures will likely occur. ExMC manages the *Risk of Bone Fracture* by assessing and mitigating the risk of fracture during a mission and during a not-yet-defined period immediately after return to Earth. HHC manages the *Risk of Early Onset Osteoporosis Due to Spaceflight* by assessing and mitigating the risk of fracture during the long-term health period after the mission. The modalities and medical tests used to assess changes to bone mineral density and other measures of bone quality are applicable to both the Fracture and Osteo risks. Hence, overlap between Fracture and Osteo research tasks is to be expected.

Osteoporosis is a condition of low mass and microarchitectural disruptions in the bone that increases the risk of fragility fractures, i.e., fractures that can occur with low or no applied loads. Osteoporosis typically manifests in geriatrics because it is often the result of slow, chronic bone loss due to the aging. Because astronauts are young, healthy and with high bone mass before they participate in space missions, fractures due to osteoporosis (i.e., fragility) would more likely occur after they return to Earth as opposed to during the mission.

It is possible that bone atrophy during spaceflight will require mitigation to prevent fractures, but we have not yet determined the time course of in-flight bone changes. Furthermore, we have not fully defined the time course of post-flight recovery or individual susceptibility to multiple risk factors that are required to determine the probability of bone fracture per individual astronaut. Space and Clinical Operations Division surveys the astronauts using widely applied clinical tests

for osteoporosis. This program also addresses the current bone standards for astronaut skeletal health, which they base on diagnostic guidelines used clinically for age-related osteoporosis. Policy-makers for age-related osteoporosis and bone densitometry suggest that these standards are not useful for assessing skeletal integrity in the younger astronaut population after prolonged spaceflight exposure. Therefore, investigators are assessing astronaut osteoporosis using novel surrogates for skeletal health derived from studies of fractures in terrestrial populations. To date, research technologies have detected spaceflight effects on the skeleton that current surveillance testing cannot detect.

The overarching approach to address the osteo risk is to (1) monitor the combined skeletal effects of spaceflight and aging; (2) determine the fracture probability for individual astronauts based on risk factors; and (3) determine the skeletal indicators that will drive countermeasure implementation to prevent premature age-related fractures in the astronaut. (Point 3 is based on Expert Opinion Level 4 Evidence — due to the inability to reach the gold standard of evidence from a prospective study of fractures in a limited number of astronauts.) To this aim, the role of the HHC Element is to conduct the measurements that fully describe the skeletal effects of spaceflight. Additionally, HHC develops, validates, and delivers countermeasures to mitigate the integrative effects of spaceflight (e.g., muscle atrophy, exposures to ionizing radiation, dietary constraints) that contribute to the premature onset of osteoporosis and fragility fractures.

4.3.3 Risk of Cardiac Rhythm Problems (Short Title: Arrhythmia)

Although a review of published reports and available data reveals some notable observations of cardiac arrhythmias during spaceflight, there appears to be no clear evidence of increased risk of arrhythmia in spaceflight missions completed to date. Existing practices that screen for the presence of clinically-significant arrhythmias and cardiovascular disease during astronaut selection and before missions likely mitigate this. Factors that might contribute to arrhythmias during spaceflight include pre-existing arrhythmias or occult cardiovascular disease before launch, age and sex of the astronauts, fluid and electrolyte disturbances, physical and psychological stress, inappropriate dietary and exercise habits, and increased levels of oxidative stress and inflammation. Some arrhythmias, such as atrial fibrillation, can develop with aging; periodic screening of astronauts during and after their active flight status will help determine whether spaceflight has long-term health consequences. Currently, there are insufficient follow-up data from astronauts completing long-duration missions in low Earth orbit to assess whether there is an increased risk of arrhythmias and cardiovascular disease as a result of these spaceflight environment exposures.

Current evidence does not support an increased arrhythmia risk during spaceflight durations up to the standard ISS length missions in low Earth orbit. Recently reported results from a prospective study designed to investigate the incidence of arrhythmia during 4-6 month missions to ISS suggest that arrhythmia burden does not increase during spaceflight, although the number of ectopic beats substantially increased in two of thirteen crewmembers. While current medical screening practices mitigate arrhythmia risk in the majority of astronauts, the authors of that study have suggested that there may be a subpopulation of individuals with a higher degree of susceptibility. However, it is unknown, whether the risk of developing cardiovascular disease – which may be manifest as arrhythmias – is increased in deep space as a result of the additive or

synergistic effects of radiation. Currently, all research relating cardiovascular disease risk related to radiation exposures is conducted under the leadership of HRP's Space Radiation Element in order to determine if this is the case.

4.3.4 Risk of Injury and Compromised Performance Due to EVA Operations (Short Title: EVA)

Astronauts perform spaceflight EVAs in confined spaces that must provide the same life support, nutrition, hydration, waste disposal, and consumables of an actual space vehicle, while allowing them to perform tasks within acceptable limits of human performance and comfort. The physiological and functional demands during EVA or EVA training can injure an astronaut, compromise their physical and/or cognitive performance, and may lead to incomplete mission objectives. Factors affecting EVA crewmember health and performance include EVA task design and concepts of operations (e.g. EVA frequency, duration); suit sizing and in-flight anthropometric changes; crewmember muscle, aerobic, sensorimotor and cognitive performance; availability of suit system and physiological sensor information (e.g., biofeedback, decision support systems); suit design parameters (e.g., suit pressure, mass, center of gravity, joint mobility, nutrition, and hydration).

Multiple planned and ongoing research studies associated with these aspects of the EVA risk were included in previous versions of the HRP but have since been defunded by the Human Research Program. These tasks are now documented in the "Integrated EVA Human Research Plan" (Abercromby et al, 2019).

4.3.5 Risk of Decompression Sickness (Short Title: DCS)

Space exploration missions will have different variables that affect decompression sickness (DCS) than Shuttle or ISS missions. This includes differences in cabin pressures, oxygen concentrations, EVA metabolic profiles, ground reaction forces, lower body musculoskeletal workloads, gravity levels, suit pressures, suit gas mixtures, and EVA durations and frequencies. DCS (even for a few days) during a lunar or exploration mission could have severe impacts on an astronaut's health and on the success of the mission.

Space exploration is remote and standard treatment methods for DCS will be unavailable. It may take months for the crew to return to Earth for treatment, therefore NASA will predominantly mitigate the risk of DCS using preventative measures.

Research tasks associated with understanding, quantifying, and mitigating the risk of DCS during spaceflight were included in previous versions of the HRP but have since been defunded by the Human Research Program. Several of these tasks are described in the "Integrated EVA Human Research Plan" (Abercromby et al, 2019).

4.3.6 Risk of Adverse Health Event Due to Altered Immune Response (Short Title: Immune)

Recent investigations have found that certain aspects of immunity are dysregulated during spaceflight and the phenomenon persists for the duration of a six-month mission. To date,

experts have characterized this phenomenon as consisting of altered peripheral leukocyte distribution, diminished T cell and NK cell function, and dysregulated cytokine profiles. Immune dysregulation is credited with the reactivation of latent herpes viruses in astronauts, likely resulting from reduced function of cytotoxic T cells. Moreover, it appears that certain adverse medical events occur in select crewmembers – including atypical allergic symptoms, atopic dermatitis, or various infectious processes – may relate to immune dysregulation. Although these phenomena have not resulted in widespread clinical concerns during orbital missions, the data suggest that astronauts will have an elevated risk for more serious adverse medical events during deep space exploration missions. Immune dysregulation is likely to worsen during such missions due to synergy with increased levels of radiation exposure, stress, and circadian misalignment, and also because treatment options will be limited with no capability for rapid return to Earth. The immune system is complicated, consisting of many distinct types of cells, each with a unique function. Current investigations continue to characterize previously uninvestigated aspects of immunity in ISS astronauts including innate cellular function, DNA damage in immune cells, gene expression in leukocytes, and protein alterations. After characterization, the HRP will determine specific clinical risks for deep space missions, develop a monitoring strategy, and determine the need and nature of potential immune countermeasures. A recent published review details options for immune countermeasures, including nutritional supplements, augmented exercise, stress relief, and pharmacological interventions (Crucian et al, Frontiers, 2018). A specific countermeasures protocol, suitable for validation in both ground analog and spaceflight conditions, is in development by the same international team of authors. In parallel, researchers are also studying immune responses of subjects who are exposed to environments that are analogous to space – including 'overwinter' (one-year duration) inhabitants of research stations in Antarctica – to aid in characterizing these in-flight phenomena and provide a terrestrial platform in which NASA could evaluate potential countermeasures.

4.3.7 Concern of Intervertebral Disc Damage upon and immediately after re-exposure to Gravity (Short Title: IVD)

Evidence has suggested that astronauts have a higher incidence of intervertebral disc (IVD) damage than the general population. On-going postflight surveillance of astronaut cohort however has not established increased incidence of IVD damage in astronauts. Studies have attempted to characterize the effects of spaceflight on the vertebral unit (vertebral bodies/IVD/musculature) but likewise the data has not further informed the concern for IVD damage. The HRP may need to expand its characterization to the entire back/spinal unit. These findings may better inform the need for in-flight countermeasures and provide the guidance to design re-entry and post-flight protocols, as well as future re-entry protocols for exploration spacecraft, as appropriate.

4.3.8 Concern of Clinically Relevant Unpredicted Effects of Medication (Short Title: PK/PD)

Research on this concern has been put on hold and will resume when determined appropriate. Pharmacokinetics (PK) is defined as the study of the time course of drug absorption, distribution, metabolism, and excretion; clinical pharmacokinetics is the application of pharmacokinetic principles for safe and effective therapeutic management of patients. The primary goals of

clinical pharmacokinetics are enhancing drug efficacy and decreasing drug toxicity. Pharmacodynamics (PD) refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. Combining knowledge of drug potency, PK, and PD, enables us to assess the efficacy and safety of medications. Studies of in-flight medication use (e.g., flight medical data mining, medication tracking, PK/PD flight studies) could provide essential knowledge regarding drug efficacy, therapeutic response, and potential impacts to PK/PD, which we need to understand to accurately assess medication safety and effectiveness during spaceflight. This concern is based on knowledge of demonstrated spaceflight effects on human physiology that would logically alter the pharmacology of administered medications. Because of the physiological changes that occur during spaceflight, it seems likely that pharmacokinetics (PK) (how the body handles administered medication) and possibly pharmacodynamics (PD) (how administered medication affects the body) could be different during spaceflight. Knowledge of in-flight medication use, efficacy, and side effects is expected to provide preliminary information on these points.

4.3.9 Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Spaceflight (Short Title: Sensorimotor)

Exposure to microgravity induces adaptive central reinterpretation of visual, vestibular, and proprioceptive information. These changes are most prevalent during and after gravitational transitions, and lead to performance decrements during and after spaceflight. During these adaptation and readaptation periods, disturbances in perception, spatial orientation, posture, gait, eye-head, and eye-head-hand coordination occur that disrupt an astronaut’s ability to control vehicles and complex systems and to move around and perform tasks. The risk of impairment is greatest during and soon after gravitation transitions when performance decrements may have high operational impact (control of vehicles during landing, immediate egress, and extravehicular activities following landing). Alterations in sensorimotor performance are a concern for Mars missions as well as extended lunar missions when astronauts will be exposed to prolonged periods of microgravity during transit and will have to perform landing tasks when they arrive. Therefore, we are currently working to define this risk more completely, including characterizing post-flight deficits in the first 24 hours after landing and investigating spaceflight-related changes (including radiation exposure) to brain structure, which might subsequently result in changes in cognition and performance of tasks. Recent results indicate that functional tasks requiring a greater demand for dynamic control of postural equilibrium (standing from a prone position after a fall, obstacle avoidance during walking, moving objects from one location to another, jumping down from a low platform and climbing a ladder) showed the greatest decrement in pre to postflight performance. These changes in functional performance were accompanied by similar decrements in sensorimotor physiological tests such as dynamic posturography and tandem walk. In addition, bed rest studies have revealed that aerobic and resistance exercise alone is not sufficient to mitigate decrements in postural stability induced by body unloading indicating the need for targeted countermeasures for post-flight postural and gait disturbances. Near-term investigations are also being planned to characterize basic neurovestibular changes during and after longer duration missions (i.e. 1 year ISS). Currently, operational countermeasures are being developed to address balance and locomotor deficits as

well as motion sickness post-flight. This includes a training protocol designed to facilitate astronauts' ability to adapt their sensorimotor responses. Future plans include defining sensorimotor standards, developing countermeasures for eye-head coordination and manual control, and developing tools for assessing sensorimotor responses and rehabilitating astronauts after spaceflight. HHC is working with HFBP and SR in support of the Integrated CBS plan (see section 4.2.1).

4.3.10 Risk of Impaired Performance Due to Reduced Muscle Mass, Strength & Endurance (Short Title: Muscle) and Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity (Short Title: Aerobic)

An astronaut's risk of impaired physical performance is in part due to reduced muscle mass, strength, and endurance and to reduced aerobic capacity. Effective exercise countermeasures (exercise hardware and the exercise prescriptions) are the primary strategies to mitigate both risks. Sensorimotor and neurovestibular impairments also contribute to reduced physical performance. Loss of aerobic fitness and muscle performance capabilities are normal physiological responses to unloading in space or spaceflight analogs. These adaptations to reduced gravity are problematic because crewmembers must maintain a certain level of performance capabilities to complete mission critical tasks in partial gravity (i.e. Mars or Moon) and in 1-G when they return to Earth.

Astronauts lose an average of 17% of their maximal aerobic capacity (VO_2pk) within the first two weeks of spaceflight. Values remain significantly below preflight levels throughout their mission and for the first 15 days after spaceflight; levels return to preflight levels by 30 days after the flight. Importantly, individual responses vary considerably: some astronauts are able to maintain preflight aerobic fitness levels during flight, whereas others experience >20% declines. These data have been reported previously in the *In-Flight VO2max Study* results (PI: Dr. Moore, HRP report and peer reviewed manuscripts). Astronauts lose an average of 5-20% of their preflight upper and lower leg muscle strength during spaceflight. Similar to the aerobic fitness data, individual response in muscle strength is highly variable: upper and lower leg muscle strength varies from no loss to 30%. These data are reported in peer-reviewed publications by K. English and S. Lee and in the recently completed Adherence to the exercise prescription and pre-flight fitness levels explains some, but not all of the individual variability. The *In-Flight Sprint Study* (PI: Dr. Ploutz-Snyder) final results will provide information to update the In-Flight VO2max study data based on new exercise prescriptions and exercise hardware, and may provide insight towards understanding individual responses. Data from astronauts and bed rest subjects are currently being analyzed to evaluate exercise-training parameters (load, intensity, time, frequency) required to maintain aerobic fitness levels and muscle strength during unloading. Current work standard development for exploration mission tasks will define the aerobic fitness and muscle strength required to perform mission critical tasks in different gravity levels (e.g., landing egress, partial gravity EVAs and ambulation, microgravity EVAs). These standards will provide information necessary for programs to develop requirements for systems and hardware (e.g. spacesuits, ECLSS, exercise hardware) needed to maintain these performance capabilities.

4.3.11 Risk of Orthostatic Intolerance During Re-Exposure to Gravity (Short Title: OI)

About 20-25% of Space Shuttle crewmembers and more than 60% of the crewmembers who participate in long-duration missions (4-6 months) experience hypotension and presyncope during a10-minute 80° head-up tilt test on landing day. The current suite of countermeasures to mitigate orthostatic intolerance during re-exposure to gravity includes on-orbit exercise, suit cooling, end-of-mission fluid loading, recumbent posture during re-entry and landing, and lower body compression garments. Additionally, medical personnel provide ground support at the vehicle landing site and administer intravenous fluids, as needed, to mitigate blood volume loss. Some astronauts will continue to wear lower body compression garments for several days after landing to manage symptoms.

4.3.12 Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS) (Short Title: SANS)

Through 2019, twenty-eight crewmembers who participated in long-duration space missions have experienced structural and/or functional changes to their eyes that include optic-disc edema, globe flattening, choroidal folds, and hyperopic shifts, cotton wool spots, and retinal hemorrhage. NASA has termed the risk of developing these ocular changes the *Spaceflight Associated Neuro-ocular Syndrome (SANS)*. Not all of these effects develop in affected crewmembers. The percentage of affected crewmembers varies for each symptom: optic disc edema, 10/74 (14%); cotton wool spot, 7/74 (10%); retinal and/or choroidal folds, 12/58 (21%); globe flattening, 17/58 (29%); retinal hemorrhage, 3/74 (4%); and change in refractive error ≥0.75D, 10/58 (17%). It is thought that the ocular structural changes are triggered by the cephalad-fluid shift that crewmembers experience during weightlessness, but because not all crewmembers develop SANS, it is likely that some environmental, genetic, anatomical, or lifestyle related factors incur greater susceptibility or protection to SANS.

Hypotheses to explain deficits in visual acuity and structural changes in the eye include elevated pressure in the cephalad vein and increased resistance in outflow from the eye veins, increased intracranial pressure, localized elevation of cerebrospinal fluid pressure within the sheath of the orbital optic nerve, and impaired drainage in the cephalad lymphatic system. The goal of several ongoing and future research is to test these hypotheses.

Many of the symptoms of SANS that develop during spaceflight recover on return to 1G; however, some structural changes are permanent or do not fully recover. It is currently unknown whether these structural changes will cause long-term decrements in visual acuity, visual fields, or have other functional consequences. Follow up imaging and testing of affected and non-affected crewmembers is currently ongoing to determine if the rate of ocular functional decrements increases years after the initial physiologic insult.

4.3.13 Risk of Adverse Health Effects Due to Host-Microorganism Interactions (Short Title: Microhost)

While current preventative measures limit the presence of many of the medically significant microorganisms during a mission, infections cannot be completely eradicated. Evidence indicates that certain characteristics of microorganisms are altered when microbes are cultured in spaceflight. These alterations include changes in virulence (disease-causing potential). Because

of this evidence, the HRP plans to compare microbial diversity, microbial characteristics, and specific host-microorganism interactions in spaceflight and ground-based conditions in close collaboration with NASA's Space Biology Program and by integrating the research between the microhost, food, and immune disciplines. This comparison, in combination with evidence from investigations of potential changes in crew susceptibility, will be used to determine the risk of microbiologically-induced adverse health effects during a spaceflight mission. Using this microbial risk assessment, the HRP will determine whether current operational and engineering controls used to mitigate these microbiological risks during human exploration of space are adequate or additional countermeasures should be developed.

4.3.14 Risk of Performance Decrement and Crew Illness Due to an Inadequate Food System (Short Title: Food)

The space food system and the nutrition it delivers is one of the most significant modifiable factors to improve human health and performance during space exploration. As mission duration and distance from Earth increase, and medical capabilities decrease, the importance of optimizing the health promoting potential of the food system as a countermeasure to physiological and psychological decrements will increase.

The space food system currently consists of processed and prepackaged foods that are required to be stable at room temperature for multiple years prior to consumption. Food may be prepositioned for a mission to Mars, with no resupply, and possibly with no refrigeration, which will require nutritional and quality stability for at least five years. Despite the potential 2-3 year length of these missions, the food will be more limited in variety and choice than it currently is on 6-month ISS missions. Recent studies have shown that the processed and shelf-stable foods used on the ISS will only retain acceptable quality and nutrition for one to three years under ambient storage conditions. Insufficient nutritional support, whether due to inadequate food system content (e.g., calories, specific nutrients, bioactive compounds), food and nutrient degradation over time, or inadequate intake by the crew may negatively impact crew health and performance. Unacceptable food, either due to quality loss over time or menu fatigue due to limited variety, could also lead to under-consumption, body mass loss, muscle loss, and eventually nutritional deficiency(ies) that may affect biochemical, physiological, or even psychological state.

Beyond nutritional and quality challenges, food mass and volume will be a significant resource burden for exploration missions. If food system requirements exceed the capabilities of the mission resources, the mission may not be feasible, or allocation of resources to other systems may be unduly constrained. Nutritional content and food quality must remain key requirements in any food system strategy to reduce mass and volume.

Several studies are underway or planned to determine how formulation, processing, packaging, and storage strategies can help increase the shelf life of a prepackaged food system and/or reduce mass and volume requirements. Alternative strategies, such as inclusion of bioregenerative salad crops, introduce new resource challenges (e.g., food safety, reliability), but offer potential solutions to nutrition and variety challenges. Delivery of personalized nutrition through automated bulk processing may also have potential to supplement the food system. Ongoing

collaborative studies are investigating the potential of food system improvements to enhance physiological and psychological health. These efforts could lead to the design of more efficient, targeted dietary interventions. Results from these studies will help to determine an optimal food system strategy and will identify areas where additional research is required to improve shelf life or food system composition.

Human history documents that exploration food system adequacy becomes more central to any mission success, especially as length and isolation increases. Food and nutrition are often the key to success (or failure) of a mission. The inadequacy of the current space food system for exploration missions is a significant risk to human health and performance, and thus to mission success. The food system for a successful exploration mission will need improved technologies and accurately defined requirements for nutrition, quality, and safety that will also support psychosocial health and nutritional adequacy with varied crew preference. In short, the space food system must be safe, nutritious, and acceptable for all phases of an exploration mission, while staying within resource constraints, to promote crew health and performance and assure mission success.

4.3.15 Risk of Reduced Crew Health and Performance Due to Hypobaric Hypoxia (Short Title: Hypobaric Hypoxia)

Future human exploration missions will require a robust and flexible EVA architecture that existing operational denitrogenation protocols, suit egress/ingress methods and EVA suit hardware do not currently provide. This robust EVA architecture can be achieved through the combination of an intermediate staged atmosphere of 8.2 psia and 34% O_2 in the habitat, variable pressure EVA suits that are compatible with a 8.2 psia habitat pressure, and highly efficient EVA ingress and egress. Oxygen enrichment in the habitat is currently limited to 34% to reduce the risk of flammability, but this enriched environment is mildly hypoxic to humans. Astronauts will inhale partial pressure of O_2 (P_IO_2) of 128 mmHg. Astronauts have experienced this P_IO_2 in space before – the Space Shuttle atmosphere was 10.2 psia / 26.5% O_2 (P_IO_2 = 127 mmHg) – but they were only exposed to this P_IO_2 for up to 10 days.

Decreased levels of O_2 to the body's organs and systems affects all physiological functions. However, the 8.2 psia and /34% O_2 environment induces only mild hypoxic stress, which healthy individuals can tolerate well on Earth. For example, millions of people live at altitudes higher than 4000 ft. and even more people experience mild transient hypoxia during airplane flights at 5000-8000 ft. However, additive effects of an 8.2 psia and 34% O_2 environment and other spaceflight factors, such as microgravity, elevated CO_2, mission stress, space radiation, and cycling between mild hypoxia and mild hyperoxia during EVA, might impair human health and performance, although this has not been established.

Should the 8.2 psia and 34% O_2 become the baseline for exploration missions, we need to understand how varying periods of exposure to this level of hypobaric hypoxic stress affects the astronaut. Using data from past shuttle flights that operated at a mild hypobaric hypoxic environment for short durations of time, we can evaluate how the increased hypobaric stress contributes to the overall physiological stress associated with this engineered environment, however, the data from Shuttle is limited and exploration scenarios could vary significantly from

our Shuttle experience. In addition, an inflight surveillance program may need to be developed to understand if and how this mild hypobaric hypoxia affects astronauts for increased durations of time.

4.4 Space Radiation

4.4.1 Risk of Radiation Carcinogenesis (Short Title: Cancer)

Given that crewmembers are exposed to radiation from the space environment, there is the possibility for increased cancer morbidity or mortality over their lifetime. Due to changes in resource availability, SR realigned the Cancer research to focus near-term efforts on testing potential risk mitigating medical countermeasures. We will monitor advances in terrestrial cancer detection and treatment, utilizing findings from the 2017 Potomac Institute report entitled "Projection of U.S. Cancer Mortality and Incidence Rates" to guide risk estimates and future research efforts. The use of the NASA Space Radiation Laboratory (NSRL) Galactic Cosmic Ray (GCR) Simulator to understand mixed field and dose and dose-rate effects on cancer risk estimates will be performed as part of a broader effort to design, test and validate the GCR Simulator which is being developed as a high fidelity analog of the space radiation environment. Further research that supports reduction in the uncertainties in risk projections through the development of tissue specific quality factors and elucidating the role of non-targeted effects will be performed as secondary goals when feasible, however, extensive tissue banking efforts from ongoing studies will be available to support future analyses.

As there are distinct mechanisms of cancer induction across and within major tissue sites, uncertainty reduction requires tissue specific risk estimates. NRA and NASA Specialized Center of Research (NSCOR) tasks focused on the major sites of lung, breast, colon, the blood system (leukemias), liver, and brain are being completed. Understanding differences in radiation sensitivity based on genetic and epigenetic factors aids the development of tissue-specific cancer models, the identification of biomarkers of both risk and early disease detection, and the identification of medical countermeasures will rely on advances in terrestrial cancer research.

Risk modeling efforts are incorporating a multi-ensemble risk assessment approach and will focus on development of methods for integrating multiple disease endpoints in risk of exposure-induced death (REID) and disease-free survival year predictions. Epidemiological studies assessing sex dependence in risk estimates for radiogenic cancers are being addressed through support of the Million Person Study. The cancer rate is the key quantity in the evaluation, representing the probability of observing a cancer at a given age and years since exposure. The life-span study of the Japanese survivors of the atomic bomb is the primary source for gamma ray data. More recently, however, meta-analysis of data for several tissue types from patients exposed to radiation or reactor workers has become available. These newer data will be used to compare with the Japanese data. Other assumptions in the model are made with regard to the transfer of risk across populations, the use of average rates for the U.S. population, age, and age-after exposure dependence of risk on radiation quality and dose rate, etc. Estimated incidence rates, mortality rates, and lifespan data in future healthy populations will be assessed in ensemble risk modeling efforts to understand health risks in the post Mars-mission era.

Determining the shape of the dose-response model for cancer induction is enumerated in biological terms through various cancer gaps. In the National Council on Radiation Protection (NCRP) model, the relationship between dose and response is linear and the slope coefficient is modulated by radiation shielding. Models of non-targeted cancer risk describe processes by which cells traversed by HZE nuclei or protons produce cancer phenotypes in regions of tissue not limited to the traversed cells. Non-targeted effects are the major mechanism that has been identified that is in disagreement with the NCRP model, and they show a non-linear dose response. The implications of such a dose response for cancer risk are large since such a model predicts a reduced effectiveness for radiation shielding. The importance of mission length is also affected by the non-linear dose response. For some cancer sites and exposure conditions, for example proton exposures, the NCRP model may be adequate. Limited NSRL research is focused on reducing the uncertainties in the model through the establishment of tissue-specific models of human cancers and on collection of data at the NSRL.

Systems biology models provide a framework to integrate mechanistic studies of cancer risk across multiple levels of understanding (molecular, cellular, and tissue). Limited *-omics* data sets and the archiving of tissue samples will be collected for future analyses. However, the development of systems biology models to improve the descriptions of cancer risk will rely on terrestrial cancer research.

4.4.2 Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (Short Title: CNS)

SR is working with HFBP and HHC in support of the Integrated CBS plan to address acute (in-mission) CNS effects from radiation exposure (see 4.2.1). Late neurodegenerative conditions are considered under the “Degen” risk (4.4.3).

4.4.3 Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure and Secondary Spaceflight Stressors (Short Title: Degen)

Degenerative tissue (non-cancer) adverse health outcomes such as cardiovascular and cerebrovascular diseases, cataracts, diseases associated with accelerated aging, digestive and endocrine disorders, and immune system and respiratory dysfunction are documented following exposure to terrestrial sources of ionizing radiation (e.g., gamma-rays and x-rays). In particular, cardiovascular pathologies such as atherosclerosis and cerebrovascular disease are of major concern following gamma-ray exposure. This evidence suggests a concern for possible degenerative tissue effects following exposures to GCR or solar particle events (SPEs) expected during long-duration spaceflight. Specifically for a Mars mission, the accumulated dose is sufficiently high that epidemiology data and preliminary risk estimates suggest a higher risk for cardiovascular diseases, and therefore this is the Element’s highest priority research area under the degenerative disease risk. However, the existence of thresholds at lower doses, the impact of dose-rate and radiation quality effects, as well as mechanisms and pathways, are not well-characterized. Degenerative disease risks are difficult to assess because multiple factors, including radiation, are believed to play a role in the etiology of the diseases. In particular, risk factors associated with lifestyle such as obesity, alcohol, and tobacco use can lead to similar adverse outcomes, clouding population-based risk estimates in the lower dose ranges and

contributing to the large uncertainties. Data specific to the space radiation environment must be compiled to quantify the magnitude of these health risks to update the current Permissible Exposure Limits (PELs), quantify the impact to disease-free survival years, and determine if additional protection or mitigation strategies are required. The possibility of radiation exposure interacting with other secondary spaceflight stressors is also being evaluated.

4.4.4 Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (Short Title: ARS)

Mission operations, monitoring, and storm shelter provisions minimize the risk of a large exposure to crew members from a SPE. However, a variety of acute radiation syndromes would be of concern following an unavoidable large SPE exposure: radiation sicknesses, such as the prodromal risks, include nausea, vomiting, diarrhea, and fatigue. These effects are manifested within 4 to 24 hours post-exposure for sub-lethal doses, with a latency time inversely correlated with dose. Furthermore, there is a reasonable concern of a compromised immune system, due to high skin doses from an SPE or other in-flight factors, although the possibility of acute death through the collapse of the blood forming systems is negligible. Additionally, recent modeling results indicate that superficial areas of the cerebral cortex may sustain higher doses than the benchmark hippocampus region of the brain, which might contribute to performance impairments (see 4.2.1). Countermeasure approaches will be based on work performed for terrestrial radiation exposures. Modeling efforts and risk assessment and design tool efforts in this area are complete and have been transferred to the Advanced Exploration Systems Program and Medical Operations for implementation.

5 CONTENT IN THE HUMAN RESEARCH ROADMAP

The IRP contains detailed research plan information in a standard format, including a graphical depiction via PRR charts and specific information fields. Through the HRR the information is accessible to the public.

5.1 Risk Page

Each HRR risk or concern item has a risk page with relevant information, including short title, risk statement, context, and mitigation strategy, as detailed below. A risk rating for DRMs, a link to the PRR chart, and a listing of the gap(s) that must be addressed before each risk is mitigated are also included on each risk page.

- Short Title: assigned to the risk as a matter of convenience and is used internally within HRP.
- Risk Statement: this is the HSRB-approved Risk Statement for each risk that concisely describes specific condition of relevance to human spaceflight missions and the negative outcomes that may potentially result.
- Context: this is the HSRB-approved Risk Context for each risk that briefly describes the what, when, where, how, and why of the risk or concern by stating the circumstances and

scenario(s) considered, any known contributing factors, operational relevance, evidence or related issues to provide background information not captured in the risk statement.

- Mitigation Strategy: the approach strategy for the mitigation of the risk is outlined in this section. For instance, the strategy may be to first determine space normal physiology, then identify specific countermeasures.

Each risk's PRR chart, which shows the forecasted timeline of risk milestones for improving risk ratings, is accessed through the PRR tab on each risk page. At this time, only the Mars PRR is available in the HRR. The PRR Chart Overview, seen in Section 6, shows a general methodology used to develop the chart. The current risk rating (HSRB-approved if available) is used as the starting point. Specific highlighted risk milestones shown on the top line for the Mars DRM represent thresholds in movements of the risk ratings (e.g., red to yellow to green). Section 6 contains a PRR overview and example chart.

5.2 Gap Page

Each gap in knowledge or in the ability to mitigate each risk, as identified by the HRP Elements, is listed in the IRP. Each gap page includes a description of the gap, which typically contains the initial state and approach, a target for closure, and a listing of the task(s) that are required to address the gap.

5.3 Task Page

Each task, as identified by the HRP Elements, required to address a gap is named in the IRP. In some cases, a task may address multiple gaps within a risk or gaps across multiple risks. Each task page typically contains information on the responsible HRP Element, Principal Investigator (PI), procurement method, the task's overall aims, resources needed (e.g., ground analog or flight), and deliverable(s). The level of detail in the task information may depend on the task's maturity level, with those tasks in the near future typically having higher fidelity and more complete information compared to tasks planned farther in the future.

In some cases, organizations outside the responsible Element, such as other HRP Elements, other divisions within NASA, the Translational Research Institute for Space Health (TRISH), or even an international partner, are responsible for implementation of specific tasks in the research plan. These collaborating organizations are identified within this section and the responsible Element will coordinate with the appropriate organization in these cases.

Each deliverable in the IRP is classified by category and subcategory. The deliverable categories and subcategories are listed in the table below and briefly described in the text that follows. This information is verbatim from HRP-47069, and is reprinted in the IRP as a matter of convenience for the reader.

TABLE 1. CATEGORY OPTIONS FOR DELIVERABLES

Category	Subcategory	Example Customers	Example Deliverables
Requirement or Guideline	Vehicle/Suit Design	Vehicle/Mission Definition & Development Program	Suit Design Requirements
	Flight Rule/ MRID/Practice Guidelines	Medical/Mission Operations	Procedures, Best Practices
Technology or Tool	Systems Solutions, Prototype Hardware or Software	Medical Operations, Vehicle/Mission Definition & Development Program	Food packaging technologies, In-flight Blood Analysis Technology, User interface prototype
	Clinical Care, Medical Informatics, Human Performance Data Collection Methods	Medical Operations, Vehicle/Mission Definition & Development Programs	Training Protocol for Effective Medical Operations, Questionnaires
	Computational Models, Software	Medical Operations, OCHMO, Vehicle/Mission Definition & Development Program	Radiation Risk Assessment models, Digital Astronaut models, Net habitable volume (NHV) model
	Database	Human Research Program, Medical Operations, Vehicle/Mission Definition & Development Program	Database created by gathering existing data
	Simulation	Medical Operations, Vehicle/Mission Definition & Development Program	Decision support tool, Integrated Medical Model
Countermeasure	Prescription	Medical Operations, OCHMO	Integrated Resistance and Aerobic Training Study
	Protocol	Medical Operations, OCHMO	Prebreathe Protocol for Exploration Systems
	Prototype Hardware or Software	Medical Operations, OCHMO, Vehicle/Mission Definition & Development Program	Prototype treadmill harness for use during exercise countermeasures, computer-based training for stress management
	Pharmaceutical or Nutritional Supplement	Medical Operations, OCHMO, Vehicle/Mission Definition & Development Program	Pharmaceutical recommendations resulting from Vitamin D Study
Standard	Update	OCHMO	Nutrition Standard Update
	New	OCHMO	Lunar Dust PEL
Risk Characterization, Quantification	Evidence	OCHMO, HSRB	NRA final report, Evidence Report, Conceptual Model
Study Results	Customer Requested Study or Analysis	Vehicle/Mission Definition & Development Program	Trade Study Analysis Results and Recommendations

Requirement or Guideline

The "Requirement or Guideline" deliverable is chosen when a task will result in information that is relevant to a requirement (or requirements set) or guideline owned by another Program or to another Element. For example, the task may end up informing the requirements on the lighting spectrum in the vehicle, or the results may apply to the radiation shielding design, or conclusions may be reached that apply to the food system from nutritional risk work. These deliverables often feed the design of the vehicle and its sub-systems. As inputs to requirements, they primarily are applied in the SRR timeframe.

Technology or Tool

The "Technology or Tool" deliverable covers a broad spectrum of developments that includes hardware, software, systems solutions, new processes, inventions, innovative methods, design tools, databases, computational models, or systems simulations. These deliverables support HRP research, as well as external customers.

Countermeasure

A "Countermeasure" deliverable is a specific protocol that is developed and validated to prevent or reduce the likelihood or consequence of a risk. Countermeasures may be medical, physical, or operational entities, such as a pharmaceutical or nutritional supplement, prototype hardware or software, or specific exercise routines, respectively. A countermeasure deliverable is usually specific and extensive enough to require validation in spaceflight. For instance, if a ground task results in a spaceflight task that is called a "flight validation study," it likely is a countermeasure. Note that in some cases the countermeasure will also affect mission operations (in areas like timelines). Some general direction on this, however, is that the countermeasure usually does not affect the design of the spacecraft, and is applied in the mission operations phase as a solution to a problem; thus, the countermeasure deliverables generally affect the mission operations PDR or CDR phases.

Standard

A "Standard" deliverable often begins as a Risk Characterization, Quantification activity. Preliminary information about a risk is often incomplete. HRP would not be in a position to recommend a standard update, but preliminary information would represent a significant step toward such a recommendation. Risk Characterization tasks can feed into other tasks that also have information for standards, or they can be combined with other "Standard" deliverables to result in a recommendation for a new or updated standard.

A "Standard" deliverable is mandated when the program is ready to provide the OCHMO with a new standard or a recommended update to an existing health or performance standard. A key test of the "Standard" as a deliverable is that the program is ready to write the text for the recommended standard update. Since the standards are applied in a broad spectrum for design and operations, these deliverables can be linked to any of the system design or mission operations milestones. They should be applied as early as possible in the design phase or mission operations development phase, so, most often, they are necessary prior to SRR.

Risk Characterization, Quantification

When a task results in information that must be considered by the HSRB, medical operations community and/or OCHMO, this deliverable is used. This deliverable is applicable when it impacts the rating of the likelihood or consequence of a risk. It is also applied when the results of the study are anticipated by the space medical operations community.

Study Results

A study or analysis is requested by an HRP customer or Element. This is often a trade study that includes analysis, results and recommendations. Data mining or literature review tasks typically produce this type of deliverable.

6 PRR CHART

PRR Chart Overview:

Verify that this is the correct version.

PRR Chart Example:

Risk of Performance and Behavioral Health Decrements Due to Inadequate Cooperation, Coordination, Communication and Psychosocial Adaptation within a Team

APPENDIX A - LINK TO HUMAN RESEARCH ROADMAP

Risk, gap and task information that was formerly contained in Appendix A is now located in the HRR:

https://humanresearchroadmap.nasa.gov/

HHC Infrastructure Gaps are not linked to any of the HRP risks; they may be found by searching "GAPS" for HHC1, 2, 3 or 5.

APPENDIX B - TECHNOLOGY READINESS LEVELS (TRL) AND COUNTERMEASURE READINESS LEVELS (CRL)

Definition of Technology Readiness Levels (TRL) & Countermeasure Readiness Levels (CRL)

[from HRP Science Management Plan, HRP-47053]

Countermeasure Readiness Level (CRL)		Technology Readiness Level (TRL)
Phenomenon observed and reported.	**CRL/ TRL 1**	Basic principles observed and reported: Transition from scientific research to applied research. Essential characteristics and behaviors of systems and architectures.
Hypothesis formed to understand phenomenon. Preliminary research & occupational surveillance studies completed to evaluate hypothesis & associated parameters.	**CRL/ TRL 2**	Technology concept and/or application formulated: Applied research. Theory and scientific principles are focused on specific application area to define the concept. Characteristics of the application are described.
Hypothesis refined with spaceflight or high fidelity terrestrial analog study(s)	**CRL/ TRL 3**	Analytical and experimental critical function and/or characteristic proof-of concept: Proof of concept validation. Active Research and Development (R&D) is initiated with analytical and laboratory studies.
Countermeasure hypothesis formed and tested in animal and cellular analogs.	**CRL/ TRL 4**	Component/subsystem validation in laboratory environment: Standalone prototyping implementation and test. Integration of technology elements.
Countermeasure hypothesis formed and tested in humans and terrestrial analogs.	**CRL/ TRL 5**	System/subsystem/component validation in relevant environment: Thorough testing of prototyping in representative environment. Basic technology elements integrated with reasonably realistic supporting elements.
Countermeasure tested & validated with humans in spaceflight. Proven to mitigate risk on limited number of subjects.	**CRL/ TRL 6**	System/subsystem model or prototyping demonstration in a relevant end-to-end environment (ground or space): Prototyping implementation on full-scale realistic problems. Partially integrated with existing systems.
Flight countermeasure qualified for particular vehicle/DRM through ground or flight testing.	**CRL/ TRL 7**	System prototyping demonstration in an operational environment (ground or space): System prototyping demonstration in operational environment. System is at or near scale of the operational system, with most functions available for demonstration and test.
Flight countermeasure integrated with operational systems and mission validated through test and demonstration in spaceflight.	**CRL/ TRL 8**	Actual system completed and "mission qualified" through test and demonstration in an operational environment (ground or space): End of system development. Fully integrated with operational hardware and software systems.
Countermeasure system thoroughly demonstrated and tested in its operational environment. Thoroughly proven operationally with numerous subjects to mitigate risk(s).	**CRL/ TRL 9**	Actual system "mission proven" through successful mission operations (ground or space): Fully integrated with operational hardware/software systems. Actual system has been thoroughly demonstrated and tested in its operational environment.

APPENDIX C - LIST OF ACRONYMS

A

aBMD	areal bone mineral density

B

BEO	beyond Earth orbit
BMD	bone mineral density

C

CDR	Critical Design Review
CHD	coronary heart disease
CHMO	Chief Health and Medical Officer
CMO	Chief Medical Officer
CNS	central nervous system
CO_2	carbon dioxide
CPG	Clinical Practice Guideline
CR	Change Request
CRL	Countermeasure Readiness Level
CSA	Customer-Supplier Agreement

D

DCS	decompression sickness
DOE	Department of Energy
DNA	deoxyribonucleic acid
DRM	Design Reference Mission
DXA	Dual-energy x-ray absorptiometry

E

EVA	Extravehicular Activity
ExMC	Exploration Medical Capability

F

FAP	Flight Analogs Project
FDA	Food and Drug Administration
Fe^0	elemental iron
FOR	Factor of Risk

G

G	gravity
GCR	galactic cosmic rays

H

H_2O	water
HCI	human-computer interaction
HEOMD	Human Exploration and Operations Mission Directorate
HERA	Human Exploration Research Analog
HFBP	Human Factors and Behavioral Performance
HHC	Human Health Countermeasures
HIDH	Human Integration Design Handbook
HRP	Human Research Program
HRPCB	Human Research Program Control Board
HRR	Human Research Roadmap
HSRB	Human Systems Risk Board
HZE	High Charge and Energy

I

IRP	Integrated Research Plan
ISS	International Space Station
ISS FIT	ISS Food Intake Tracker
ISS UPA	ISS Urine Processor Assembly
ITI	intratracheal instillation
IVD	intervertebral disc

J

JSC	Johnson Space Center

K

L

LEO	low Earth orbit
LET	Linear Energy Transfer
LSAH	Lifetime Surveillance of Astronaut Health
LOC	Loss of Crew

M

MRID	Medical Requirements Integration Document

N

NASA	National Aeronautics and Space Administration
NCRP	National Council on Radiation Protection
NRA	NASA Research Announcement
NSCOR	NASA Specialized Center of Research
NSRL	NASA Space Radiation Laboratory

O

O_2	oxygen
OCHMO	Office of the Chief Health and Medical Officer
OI	orthostatic intolerance

P

PD	pharmacodynamics
PDR	Preliminary Design Review
PEL	permissible exposure limit

PI	principal investigator
PIO2	partial pressure of O_2
PK	pharmacokinetics
PRD	Program Requirements Document
PRR	Path to Risk Reduction
Q	
QCT	Quantitative Computed Tomography
R	
R&TD	research and technology development
REV.	Revision
RFP	Request for Proposal
RID	Review Item Discrepancy
ROI	Research Operations and Integration
S	
SA	situation awareness
SANS	spaceflight associated neuro-ocular syndrome
SBIR	Small Business Innovation Research
SMO	Supplemental Medical Objective
SPE	solar particle event
SR	Space Radiation
SRR	System Requirements Review
STD	Standard
T	
TBD	to be determined
TRI	Translational Research Institute
TRL	Technology Readiness Level
U	
UPCG	Unique Processes, Criteria, and Guidelines
VWXYZ	