Human Research Program

Integrated Research Plan

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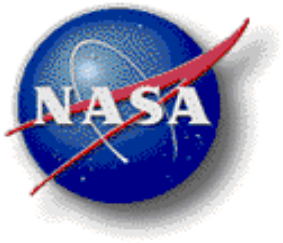
Revision R



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Human Research Program
Integrated Research Plan

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	DOCUMENT CHANGE/ REVISION LOG	PAGE 1 OF 2

Change/ Revision	**Date**	**Description of Change**	**Pages Affected**
Interim Baseline	12/20/2007	Initial Release approved by HRPCB per SLSDCR-HRPCB-07-030	All
Revision A	1/23/2009	Revision A approved by HRPCB per SLSDCR-HRPCB-08-025-R1	All
Revision B	6/24/2010	Revision B approved by HRPCB per SLSDCR-HRPCB-10-009-R2	All
Revision C	7/28/2011	Revision C approved by HRPCB per SLSDCR-HRPCB-11-010-R3	All
Revision D	7/23/2012	Revision D approved by HRPCB per SLSDCR-HRPCB-12-014	All
Revision E	7/29/2013	Revision E approved by HRPCB per SLSDCR-HRPCB-13-007 and SLSDCR-HRPCB-13-008	All
Revision E, PCN-1	9/12/2013	Revision E, Page Change Notice-1, approved by HRPCB per HHPD-HRPCB-13-016	Appendix A, HRR content
Revision E, PCN-2	12/9/2013	Revision E, Page Change Notice-2, approved by HRPCB per HHPD-HRPCB-13-021	Appendix A, HRR content
Revision E, PCN-3	2/6/2014	Revision E, Page Change Notice-3, approved by HRPCB per HHPD-HRPCB-14-004	Appendix A, HRR content
Revision F	7/28/2014	Revision F approved by HRPCB per HHPD-HRPCB-14-018	All
Revision F, PCN-1	3/16/2015	Revision F, Page Change Notice-1, approved by HRPCB per HHPD-HRPCB-15-002	Appendix A, HRR content
Revision G	7/24/2015	Revision G approved by HRPCB per HHPD-HRPCB-15-019	All
Revision G, PCN-1	10/8/2015	Revision G, Page Change Notice-1, approved by HRPCB per HHPD-HRPCB-15-025	Appendix A, HRR Content
Revision G, PCN-2	1/28/2016	Revision G, Page Change Notice-2, approved by HRPCB per HHPD-HRPCB-16-001	Appendix A, HRR Content
Revision G, PCN-3	5/20/2016	Revision G, Page Change Notice-3, approved by HRPCB per HHPD-HRPCB-16-002	Appendix A, HRR Content
Revision H	7/25/2016	Revision H approved by HRPCB per HHPD-HRPCB-16-005	All
Revision H, PCN-1	9/1/2016	Revision H, Page Change Notice-1, approved by HRPCB per HHPD-HRPCB-16-007	Appendix A, HRR Content

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Revision H, PCN-2	10/28/2016	Revision H, Page Change Notice-2, approved by HRPCB per HHPD-HRPCB-16-010	Appendix A, HRR Content
Revision H, PCN-3	12/13/2016	Revision H, Page Change Notice-3, approved by HRPCB per HHPD-HRPCB-16-012	All
Revision H, PCN-4	6/1/2017	Revision H, Page Change Notice-4, approved by HRPCB per SA-00035	Appendix A, HRR Content
Revision I	7/25/2017	Revision I, approved by HRPCB per SA-00186	All
Revision I, PCN-1	11/29/2017	Revision I, Page Change Notice-1, approved by HRPCB per SA-00459	4.3.12, Appendix A, HRR Content, and Appendix C, List of Acronyms
Revision I, PCN-2	3/27/2018	Revision I, Page Change Notice-2, approved by HRPCB per SA-00678	Appendix A, HRR Content
Revision J	7/30/2018	Revision J, approved by HRPCB per SA-00943	All
Revision J, PCN-1	3/13/2019	Revision J, Page Change Notice-1, approved by HRPCB per SA-01361	Appendix A, HRR Content
Revision K	7/31/2019	Revision K, approved by HRPCB per SA-01828	All
Revision L	7/23/2020	Revision L, approved by HRPCB per SA-02844	All
Revision L, PCN-1	11/20/2020	Revision L, Page Change Notice-1, approved by HRPCB per SA-03293	Appendix A, HRR Content
Revision L, PCN-2	3/25/2021	Revision L, Page Change Notice-2, approved by HRPCB per SA-03728	Appendix A, HRR Content
Revision M	7/22/2021	Revision M, approved by HRPCB per SA-04069	All
Revision M, PCN-1	4/17/2022	Revision M, Page Change Notice-1, approved by HRPCB per SA-04867	Appendix A, HRR Content
Revision N	7/27/2022	Revision N, approved by HRPCB per SA-05219	All
Revision O	12/8/2022	Revision O, approved by HRPCB per SA-05471	Appendix A, HRR Content
Revision P	7/24/2023	Revision P, approved by HRPCB per SA-06306	All
Revision Q	11/29/2023	Revision Q, approved by HRPCB per SA-06718	Appendix A, HRR Content
Revision R	5/23/2024	Revision R, approved by HRPCB per SA-07116	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 all 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 (2023-2027), 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
N/A	HSRB Risk Content (https://www.nasa.gov/hhp/hsrb)

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)
JSC-66705	Human System Risk Management Plan

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.

HRP Requirements and Content Alignment

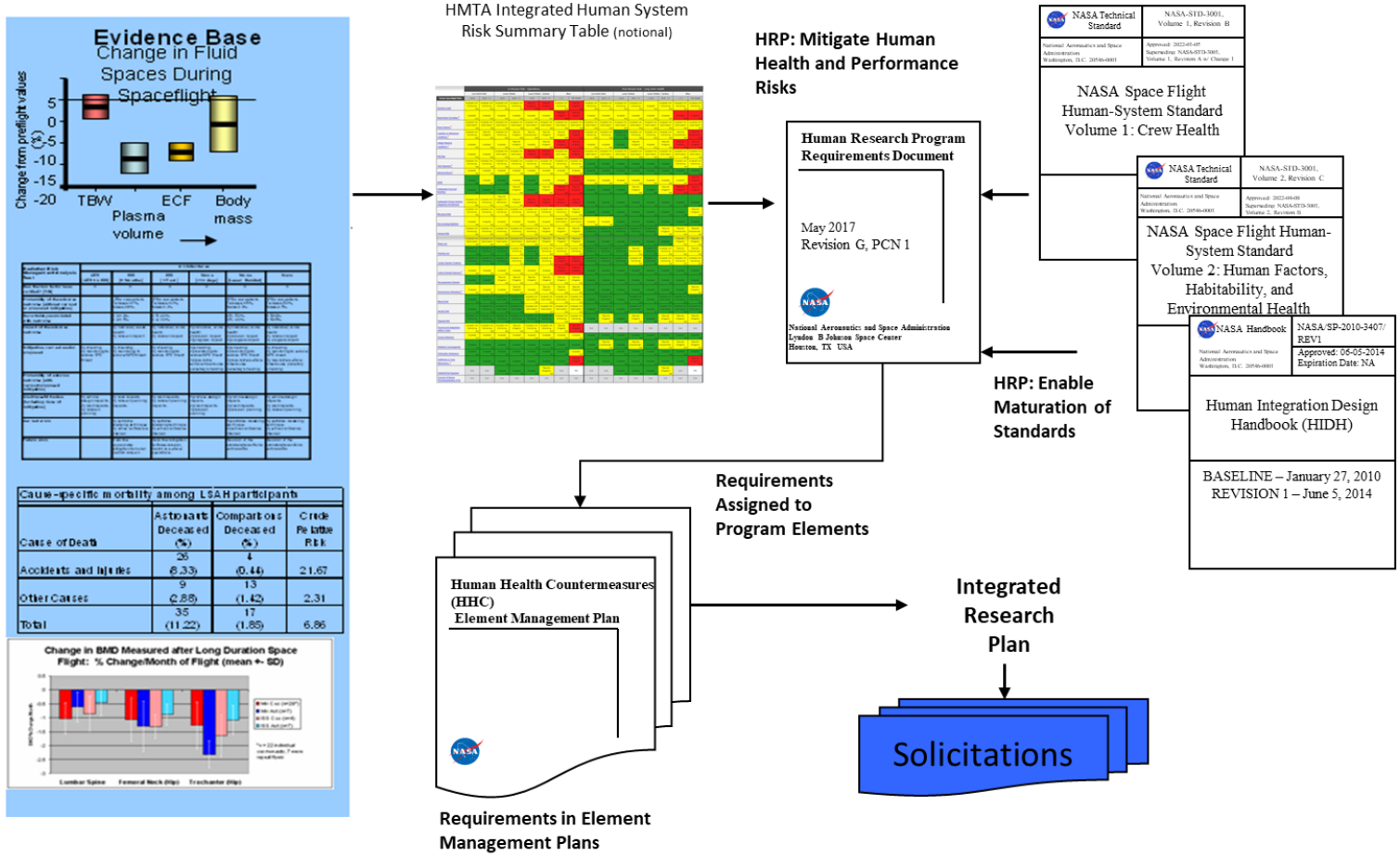


Figure 1. HRP Requirements and Content Alignment

3 CONTEXT OF THE IRP

3.1 Risk Research Portfolio

Human systems risks fall within the purview of the Health and Medical Technical Authority (HMTA) under the Chief Health and Medical Officer (CHMO). The CHMO delegates the Johnson Space Center (JSC) HMTA authority to the JSC Chief Medical Officer (CMO) and delegates JSC as the Lead HMTA Integration Center (LHIC) for Human Spaceflight. The JSC CMO established the Human Systems Risk Board (HSRB) (https://www.nasa.gov/hhp/hsrb), chaired by the JSC Human System Risk Manager, to ensure a consistent, integrated process for managing human system risks (https://www.nasa.gov/hhp/human-system-risks) that are critical to successful human exploration. Risks in the HRP research portfolio are a subset of human system risks identified by the HSRB that the HRP has decided to support with research. These risks are 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 Space Operations Mission Directorate (SOMD) and the Office of the Chief Health and Medical Officer (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 evidence by HRP Elements and discipline scientists are found in the HRP Evidence Reports in support of the integrated evidence base that HSRB maintains for this subset of HSRB risks. The HRP Evidence Reports are available to the scientific community and general public at the following link: http://humanresearchroadmap.nasa.gov/evidence/. These reports receive outside independent review and are updated as needed.

3.3.2 Risks

The HSRB, chaired by the JSC Human System Risk Manager, identifies, assesses and monitors Human System Risks on behalf of the CHMO based on current evidence. Each risk is evaluated by an integrated team of risk custodians that assesses a Likelihood and Consequence (LxC) rating and risk disposition for each Design Reference Mission (DRM) category, and for in-mission, long-term health and flight recertification risk impact categories, as applicable. These HSRB risk ratings are 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 DRM category. The agreed-upon risk ratings are maintained by the HSRB and serve as one of several inputs to inform prioritization decisions, helping HRP Management make its own decisions regarding allocation of program resources. Directed Acyclic Graphs (DAGs) are a new tool that enhances understanding and communication of risks and similarly approved by the HSRB. Each risk DAG is a causal flow representation from the spaceflight hazards that created the risk to the mission level outcomes of interest, while capturing the relationships between the intervening contributing factors. The DAGs are developed and maintained by the HSRB. The HRP uses the HSRB forum to communicate updates to the risk evidence base 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 captured in a strategy chart called the Risk Approach Plan (RAP). This chart includes a Path to Risk Reduction (PRR) bar to depict an overall timeline and significant risk milestones, along with research logic descriptions and flow chart to show the research strategy being used to improve the risk ratings.

In the past, the HRP documented some risks at a more-detailed level than the HSRB. These sub-risks were documented as standalone risks in the HRR. As part of the 2020 IRP revision (revision L), the risks documented in the HRR now align with the HSRB. Traceability information to show the transition from the past sub-risks to the current combined risks is given on the affected risk pages in the HRR.

3.3.3 Gaps

The HSRB identifies high value risk mitigation targets that describe areas of knowledge or capability needed to reduce risk. When HRP decides to address any of these areas, it identifies specific gaps in knowledge and the ability to mitigate the risk that research can address. 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 unknowns that need to be addressed 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. During FY20 the HRP Elements completed a strategic re-planning exercise on the research plans for many of the HRP Risks in the HRR. The new strategies required significant gap updates for many of the HRP Risks. The 2020 IRP revision (revision L) includes these new gap structures. Traceability information to show the transition from the old gaps to the current gaps is given on the affected gap pages in the HRR.

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. Common deliverables include recommended standards (e.g., Permissible Exposure Limit [PEL]), requirements (e.g., flight rule), risk characterization, countermeasures, tools 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 iPRR.

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 procurement mechanism in the HRR. External customers for the products delivered by HRP typically include: the NASA OCHMO, HSRB, HMTA, System Capability Leadership Team (SCLT), Crew Health & Safety (CHS), and Human Health and Performance Directorate (HHPD). Common external deliverables include recommendations for new or updated standards (e.g., Permissible Exposure Limits), requirements (e.g., Net Habitable Volume for a spacecraft), countermeasures, and technologies. Specifications for some external deliverables are agreed upon with the external customers of the HRP products.

3.4 Multi-Disciplinary Research Plans

A Multi-Disciplinary Research Plan (MDRP) is an accumulation of related research to demonstrate relationships and integration between multiple HRP risks. The documentation of an MDRP in the HRR is a new capability as part of the 2021 revision (revision M). An example of an MDRP is the Combined Behavioral Stressors (CBS) research project which integrates research topics across three high-impact risk exposures – space radiation, isolation, and altered gravity. The MDRP item is equivalent in the HRR hierarchy to a Risk, but it is **not** a risk itself. The risks integrated and any evidence documents specific to the MDRP can be viewed as part of the MDRP record in the HRR.

3.5 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 and previous research data now accessed through the NASA Life Sciences Portal (NLSP). This system provides access to the Life Sciences Data Archive (LSDA) containing plant, cellular, animal and human research data, as well as the animal biospecimen repository. The NLSP also hosts the data request portal for non-publicly available astronaut research and medical data, analog data, and animal biospecimens. Additional sources include 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 3.6.

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 2031 levy significant constraints on available flight resources. However, since not all research that requires the ISS can be accomplished by 2031, the HRP will continue to plan use of the ISS as a viable research platform should the vehicle retirement be extended beyond the 2031 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.

3.6 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.

3.7 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, tasks and MDRPs 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 or MDRP, the tasks associated with a given gap, the cross-integration of a task across multiple gaps, and deliverables associated with a task.

4.1 Exploration Medical Capability

4.1.1 Risk of Adverse Health Outcomes and Decrements in Performance Due to Medical Conditions that occur in Mission, as well as Long Term Health Outcomes Due to Mission Exposures (Short Title: Medical Conditions)

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. Each medical system designed for earlier human spaceflight was developed for a close-proximity, Earth-centered mission that enjoyed the advantages of real-time tele-medical 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 the above 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

lunar/Artemis and Mars missions, to identify operational barriers to meeting those needs, and to implement a research pathway in the support of stakeholder needs and interests.

The medical challenges expected in a Mars mission are unlike any prior human 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 exploration missions, and the trading of medical capabilities against other vehicle components within a vehicle architecture limited by mass, volume, power, data, and many other factors unique to long-distance spaceflight. Medical system requirements and vehicle design must be integrated 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. 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 evidence-based methods of monitoring and maintaining astronaut health. Essential to completing this task is the advancement in techniques that identify, prevent, and treat health threats that may occur during space missions. These techniques, in turn, must be supported by an evidence-based medical data architecture appropriate for long-duration, exploration-class missions. This exploration medical system will need to be designed for use in progressively Earth Independent Medical Operations (EIMO), so that astronauts can function autonomously to maintain their own crew health and performance.

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 quantitative evaluation of medical risk, trade space analyses of clinical capabilities, development of technical requirements, and system implementation options will be necessary.

Importantly, the medical system is just one component of a larger Crew Health and Performance (CHP) system and must integrate with other CHP systems, including Wellness, Task Performance, and Environmental Monitoring. This effort is intended to meet TH-8LM in NASA’s 2022 Moon to Mars Objectives (hyperlink to this site https://www.nasa.gov/sites/default/files/atoms/files/m2m-objectives-exec-summary.pdf).

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

Historical spaceflight data have revealed both 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 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) integrating in-flight strategies to reduce stone formation into exploration medical system designs, 2) progressively autonomous ultrasound monitoring and biochemical diagnostics for early detection of stones, and 3) treatment 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: Pharm)

NASA's current LEO operations involve frequent resupply missions that may be problematic for some long duration missions and impossible for deep space exploration missions. As such, ensuring a safe and effective pharmacy for exploration missions is an important 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 or the medications themselves affect drug pharmacokinetic and pharmacodynamic properties. The potential for drug instability compounded by altered drug response may pose a 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: analysis of medication packaging and storage solutions; studies that will provide validation for chemical / physical pharmaceutical stability; degradation product toxicity and drug safety profiles; and better characterize pharmacokinetics, pharmacodynamics, and pharmacotherapeutic properties of medications in spaceflight.

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

The impact of exposure to dust from extraterrestrial sources (celestial dusts) could lead to respiratory, cardiac, ocular, or dermal harm during exploration surface missions, resulting in immediate or long-term health effects. NASA needs to sufficiently characterize the consequences of exposure to these dusts so that vehicles and habitats are designed to maintain concentrations of airborne dust within safe limits while future operations planning minimizes the dust impacts on human health and performance. NASA rodent based research results coupled with expert review have established a permissible exposure limit (PEL) for lunar dust that has been converted into a NASA standard. This lunar dust NASA standard is being used to develop engineering controls for lunar surface missions that keep astronaut exposures below the PEL. Current research is focused on determining the allergenicity of lunar dust exposure and future work will be performed on Mars surface samples once acquired.

4.2 Human Factors and Behavioral Performance

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

Given that crews in future exploration missions will be exposed to extended durations of isolation and confinement, greater distances from Earth, as well as increased exposures to radiation and altered gravity, there is a possibility that these singular or combined hazards could lead to (a) adverse cognitive or behavioral conditions affecting crew health and performance

during the mission; (b) development of psychiatric disorders if adverse behavioral health conditions are undetected or inadequately mitigated; and (c) long term health consequences, including late-emerging cognitive and behavioral changes. Spaceflight operational challenges include, but are not limited to, increased autonomy, fatigue, reduced communication capabilities and prolonged separation from home, limited resupply, and may also contribute to the development of behavioral, cognitive, or psychiatric conditions which could negatively impact the individual, crew, and/or mission success. The magnitude of physical and biological stressors will vary by mission and mission phases but may simultaneously and/or cumulatively effect the human system with the potential to adversely impact operationally-relevant crew performance. Although anecdotal evidence indicates that longer duration missions can be fatiguing and induce stress, there has been no incidence of reported psychiatric disorders on either shuttle missions (Billica 2000) or ISS missions (Integrated Medical Model, IMM) (Myers et al. 2015). In contrast, anecdotal reports from the early (i.e., Mir and Skylabreveal that the signs and symptoms of depression and other behavioral disorders have occurred during flight and at times impacted mission objectives (Cooper et al., 1976).

During an ISS mission where two crew members spent close to one year on ISS, reductions in processing speed, visual memory, and inductive reasoning during a one year LEO mission were documented(Garrett-Bakelman, et al., 2019). An investigation of sleep, psychomotor performance, and self-report visual analog scale ratings revealed decrements in reaction time associated with reduced sleep on orbit, in addition to increasing ratings of stress over the mission duration for some crew (Jones et al., 2021). Thus, to date, while no behavioral emergencies, psychiatric disorders, or significant cognitive impairments have been reported among astronaut or analog crew, subclinical symptoms and minor deficits have been reported in a subset of individuals but have not yet resulted in a loss of mission objectives.

Whether this remains consistent or is further exacerbated during Artemis or future long duration exploration missions, where exposure to spaceflight hazards will increase and access to terrestrial support will decrease, is of primary interest to HFBP. The primary goal is to detect, monitor, and mitigate cognitive and/or behavioral health decrements to maintain astronaut health and wellbeing, as well as ensure mission success.

HFBP is developing methods and tools to monitor and detect early markers of distress and countermeasures to treat early risk factors that may contribute to adverse cognitive and/or behavioral conditions, as well as psychiatric disorders, for future exploration missions. Analogs and LEO spaceflight (where appropriate) are used to test, refine, and validate these methods and tools. Current efforts also aim to understand adverse consequences of operational stressors unique to Artemis (i.e., communication delays, altered sleep schedules), characterize meaningful change in behavioral health and performance metrics, and identify operationally relevant biomarkers for prevention early identification, and treatment of adverse behavioral conditions and psychiatric disorders. HFBP also develops countermeasures to maintain cognitive and/or behavioral health and enhance mission performance; provides recommendations for spaceflight medical operations; and, provides updates for human health and performance standards, and habitability and human factors standards.

Additionally, HFBP leads the CBS research project in collaboration with the HHC and Space Radiation Elements, which integrates research topics across three high-impact risk exposures –

space radiation, isolation, and altered gravity – that may collectively effect the central nervous system (CNS), and subsequently, crew cognition, behavior, and/or performance, as well as long term wellbeing. The translational approach aims to incorporate operational performance and fitness for duty standards to develop guidelines and deliver Performance Outcome Levels (POLs) and to leverage countermeasure development being led by the HRP elements, considering ways through which these mitigation approaches can be augmented or leveraged to prevent and/or treat potential synergistic effects resulting from multiple hazard exposures.

4.2.2 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, which includes both flight crew and ground support as part of the larger multi-team system. While relatively few empirical spaceflight studies have been conducted regarding the impact of interpersonal factors on performance, a growing body of evidence from spaceflight analog environments suggests that team-level issues could jeopardize long-duration exploration missions. Reports from spaceflight missions prior to ISS (e.g., MIR), reveal that several missions may have been terminated earlier than planned and saw a decrement in performance due in part to friction between crewmembers. Additionally, some veteran NASA astronauts have reported conflict during previous missions, while ineffective team skills have reportedly led to performance decrements and/or more training (Stuster 2010; 2016). Conversely, good team skills have benefited team cohesion, shared mental models, and performance in space. Understanding the potential impacts of inter-personal issues from spaceflight and high-fidelity analog environments is important for identifying countermeasures to aid crews and ground support during future high-autonomy missions (e.g., cislunar space and Mars).

Recent risk-characterization studies in several extreme environments 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. Current studies in spaceflight (e.g., low Earth orbit and Artemis) and high-fidelity analogs (e.g., NASA's HERA and CHAPEA, Antarctic stations) have goals of: identifying the critical drivers of team and multi-team systems functioning; validating objective measures for monitoring crew cohesion and processes; composing and supporting teams with a varying mix of knowledge, skills, abilities, and personalities; integrating varying national and organizational cultures; coordinating across the multi-team system under communication delays, and during changing levels of autonomy; informing human factors designs in habitability for a team in increased confinement, and in interactions with robotics, computers, and automated systems; developing approaches to enhance team training related to teamwork skills and multi-cultural crews; and identifying risks associated when mixing professional NASA astronauts and private astronaut missions on the same vehicle.

Deliverables build upon the current highly successful in-flight support services and countermeasures, and astronaut selection techniques, to mitigate risks associated with exploration-like increased isolation, confinement, duration, and communication delays. Near-term Artemis missions will also introduce increasing complexity in regards to distributed teams,

and team performance functions such as lunar surface extravehicular activity (EVA). Measures and countermeasures addressing the Team Risk across multiple mission types are in development to assess feasibility and acceptability in extreme environments and to examine supportive affects on crew cohesion and performance. Ultimately, a validated, cross-Risk suite of integrated countermeasures will ensure the best team composition, training, and support for multiple distributed space and Earth teams beyond low Earth orbit.

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

Objective and subjective evidence indicated that sleep was reduced to approximately six hours per night during historical missions and during the first ~15 years on the ISS. Studies identified numerous environmental challenges associated with sleep disruption, including noise, inappropriate patterns of or insufficient light exposure, uncomfortable temperature, and lack of privacy. In addition, frequent sleep shifts induced circadian misalignment as much as 20% of the time on ISS, which resulted in an hour of sleep loss compared to schedules that maintained circadian alignment. A recent study conducted on ISS suggests that crewmembers can achieve more than the recommended seven hours of sleep per night when they are provided with an optimal sleep environment and regular schedules, suggesting that neither the microgravity environment, nor the characteristics of crewmembers are responsible for the previously observed reduced sleep duration in space.

While it has now been determined that crewmembers can achieve sufficient sleep in microgravity, future Artemis and Mars missions will not provide the same environment and scheduling that is currently available on the ISS. Early Artemis missions are expected to involve high tempo workload, variable schedules, and small volume vehicles without private sleep quarters. These conditions have the potential to significantly curtail crew sleep duration and quality. Ground and flight evidence demonstrates that performance impairments can occur when individuals obtain insufficient sleep. Performing is worst when individuals must complete tasks during the biological night and sleep during the biological day.

Extended missions on the lunar surface will introduce increased exposure to radiation, which may increase the risk of circadian misalignment and disrupted sleep. Mars missions will further introduce a non-earth day-night cycle, with the Mars day of 24 hours and 39 minutes, impacting both in-mission and ground support teams.

HFBP research aims to further characterize and quantify this risk by implementing studies relevant to future spaceflight DRMs extending the information already gained through objectively measuring sleep quality and quantity, circadian phase, 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 future research studies.

Such investigations help to inform the optimal countermeasure strategy for mitigating the health and performance effects of sleep loss and related issues in flight. Current efforts aim to identify

how crewmembers use countermeasures such as caffeine to compensate for reduced sleep and to characterize the impact of air quality on sleep during spaceflight. Ongoing work involves the integration of operational protocols and technical requirements for lighting, noise, temperature, and scheduling for future exploration vehicles. Other countermeasures for mitigating risk include sleep-wake models of performance that can inform real time scheduling decisions as well as optimal ways to individualize countermeasure regimens, such as strategic use of caffeine, sleep medication, and napping. The effectiveness of other potential countermeasure strategies, relevant to future mission scenarios, may also be assessed.

4.2.4 Risk of Adverse Outcomes Due to Inadequate Human Systems Integration Architecture (Short Title: HSIA)

The Human Systems Integration Architecture (HSIA) is a conceptual framework proposed to address the integration of onboard capability with crew roles and responsibilities necessary to enable effective and efficient performance in the increasingly autonomous missions. Research in the HSIA risk area is focused on the challenges of exploration missions, i.e., beyond LEO. Laboratories/simulations, terrestrial analogs, and spaceflight missions (e.g., ISS, Artemis) serve as platforms through which exploration-specific research questions may be addressed, with areas of focus including methods through which we can support performance given increasing autonomy and communication delays. Human Factors research gaps within the framework of HSIA allows the risk to be aligned with measurable outcomes that meet the needs of future operations.

In context of future long duration missions to Mars, crew will no longer be able to depend on support from Mission Control Center (MCC) in real-time due to distance from the Earth, and will have to work increasingly autonomously, performing critical tasks that were previously carried out by Flight Controllers. This greater crew/vehicle autonomy will depend, in part on advanced, on-board automated systems but also on new approaches to training, teaming and crew support. It will also depend on successfully integrating intelligent vehicle capabilities with crew capabilities. Exploration crew-vehicle systems will have decreasing support from Earth in terms of tactical operations as well as resupply and evacuation options, compounding the new challenges for crew, and increasing risks to human performance due to the stress, fatigue, radiation exposure, and isolation that characterize these missions.

To help mitigate this risk, we need to understand the types of tasks that astronauts will likely be performing autonomously (e.g., monitoring telemetry, a job currently done by over 50 people per day on a 24/7 schedule), and develop human-system integration standards and guidelines for the needed tools and countermeasures that ensure success in performing those tasks on an autonomous mission. An HSIA approach addresses the integration of onboard capability and crew roles and responsibilities necessary to enable adequate response to safety critical situations in the required increasingly autonomous mission operations framework. *Enabling a flight crew of 4 to perform the tactical job that has traditionally been done by a ground crew of 40+ will require a fundamental rethinking of crew-vehicle integration and operations.* This mode of operation will be very different from the current dependence on frequent real-time direction from a large MCC ground support team of diverse specialties (Dempsey et al., 2018).

This new mode of operation will be particularly important when dealing with unanticipated, off-nominal situations. A delay or absence of ground support during unanticipated contingencies can become a significant hazard and can jeopardize the crew and the vehicle if no appropriate onboard capabilities exist to assist with troubleshooting and contingency management. To attain increased autonomy, crewmembers must have complementary and enhanced capabilities that will enable the 4-person flight crew to perform the kind of anomaly response that has previously been done mostly by MCC, and complete these activities in many operational contexts, including delayed communication or even unexpected blackouts.

It is important to highlight that mission systems (vehicles, habitats, suits, etc.) will experience unanticipated safety critical malfunctions, sometimes due to human error, but more often simply due to the challenges of engineering complex systems for performance in extreme environments. Artificial intelligence (AI) and intelligent, autonomous systems can help the human solve problems with complex engineered systems, however, the AI systems will not be able to provide complete problem-solving capabilities. It is therefore critical that c*apabilities be wrapped around the human(s) in order to address safety critical issues and mission events.* To further mitigate the risk, specific factors have been identified (e.g., anomaly detection/response, ground-independent procedure execution, data visualization, advanced training techniques, etc.) as highly relevant to long-duration exploration missions, and research will focus on understanding the impact of these factors on those exploration missions.

4.2.5 Risk of Injury from Dynamic Loads (Short Title: Dynamic Loads)

Crewmembers are at risk of injury from exposure to dynamic loads during the rapid acceleration and deceleration phases of a spaceflight. Dynamic loads are transient loads (lasting for less than 500 ms) that are most likely to occur during launch and landing, and during pad or launch abort, and parachute deployment.

Research on injury prevention and impact biomechanics is important for the aerospace and the automotive industries, and for athletics, and astronautics. Minimizing the risk of injury to a specific population involves assessing their environment. Although the probability of a high impact load is low when riding in a car (1 in 1.3 million miles traveled) or flying in a military aircraft (1 in 14,000 sorties), capsule-based spacecrafts expose crewmembers to dynamic loads during each flight [1, 2]. NASA takes a conservative approach to the low risk of injury during dynamic loads and incorporates adequate occupant protection standards into vehicle designs.

Several extrinsic factors affect the risk of injury from dynamic loads, including the profile of the vehicle, and the design of the seats, restraint systems, spacesuit, and helmet. Because each vehicle can have different launch, abort, and landing (terrestrial and extra-terrestrial) dynamics, the risk of injury is greatly influenced by the vehicle design. Additionally, pressurized or unpressurized planetary vehicles (e.g., lunar rovers) could introduce injury risk due to interaction with the terrain. Vehicles that minimize crew exposure to dynamic loads will be inherently safer than vehicles that induce higher dynamic loads. The seat and restraint designs may either increase or mitigate risk of injury depending on how effectively they minimize movement of the body relative to the seat and other body regions. Finally, the spacesuit and helmet may contribute to the risk of injury if the design is not configured to protect the occupant during dynamic loads.

For instance, the suit can hinder the effectiveness of the restraints, thus dynamic loads increase; rigid elements of the spacesuit can induce point loading; and the helmet can cause injury from blunt impact, or it may overload the neck muscles if the neck is not properly supported.

In addition to the extrinsic factors described above, intrinsic factors such as age, sex, anthropometric measures, and physiological deconditioning due to spaceflight can contribute to the risk of injury. Age affects the risk of injury in other situations that are analogous to spaceflight-induced dynamic loads, such as automobile collisions. Sex can influence the risk of injury from dynamic loads because men can have different body strength and have different geometry than women. Anthropometric measures can affect injury risk because loads may not be proportional to the difference in anatomical structure and strength. For example, a one size fits all flight helmet will induce a larger burden for smaller necks than larger necks. Furthermore, after crewmembers have been exposed to microgravity, they may have a lower tolerance to dynamic loads than they did at the beginning of the mission due to the spaceflight-induced physiological deconditioning that degrades the structure and response of the musculoskeletal system.

Multiple methods are available to assess the risk of injury from dynamic loads, and each method has advantages and disadvantages. These methods can be grouped into 3 categories: humans, human surrogates, and numerical models. Tests on humans would seem ideal for assessing the risk of injury because humans can provide subjective feedback, but tests on humans must be limited to sub-injurious levels only. Injury metrics can be obtained from humans who have survived accidents; however, no prospective investigations of injury mechanisms are available in these types of situations, which typically limits inference from the data. Human surrogates include post-mortem human surrogates (PMHS), anthropomorphic test devices (ATD), and animal models. PMHS can be tested at injurious levels but cannot be used to investigate how living tissue responds to trauma, and they do not include active muscle tone. ATDs are manikins that vary in biofidelity depending on the design and the loading conditions. ATDs cannot be used to predict injury in all conditions; however, tests using ATD are easy to perform and the data is reproducible. Although animal models can be used to test injury to living tissue, animals are, of course, not anatomically identical to humans, making it difficult to translate results from animals to risk of injury for humans. Numerical models can be used to assess risk of injury, although the fidelity of a model depends on the quality and the quantity of the human and the human surrogate data used to validate the model. Dynamic response models are simple but have limited capabilities for predicting injury. ATD finite element models (FEMs) have similar limitations as the actual ATD tests, but they can be used to assess cases that cannot be tested physically. Human FEMs have great potential for predicting injury but currently these models are not validated in all spaceflight loading conditions. Finally, regardless of the method used to assess the risk of injury from dynamic loads, adequate criteria for assessing low risk of injury (<5%) are needed.

Multiple knowledge gaps still exist in our understanding of the risk of injury from dynamic loads: the currently operating spacecraft has not been adequately characterized, insufficient injury metrics exist for all possible loading conditions including standing posture, no injury metrics exist that account for the differences between men and women, and the contribution of spaceflight-induced physiological deconditioning to injury risk has not been characterized. In

addition, criteria must be validated to adequately assess low risks of injury, and adequate tools are required for assessing injury risk. These knowledge gaps highlight the areas of research that are needed to mitigate this risk.

4.3 Human Health Countermeasures

4.3.1 Risk of Performance Decrement and Crew Illness Due to Inadequate Food and Nutrition (Short Title: Food and Nutrition)

The space food system and the nutrition it delivers will be critical to the success of crewed space exploration missions. During these long-duration, confined missions in the harsh environment of space, food and nutrition will be an essential countermeasure for maintaining the health and performance of astronauts. Outside of low-Earth orbit, constraints on resources and lack of food resupply will further constrain nutritional support of crew health. Increased radiation exposure on these missions will increase risks of oxidative stress and resulting tissue damage, effects which can be mitigated with optimal food and nutritional support, or exacerbated with suboptimal provisioning.

The ISS food system consists of processed and prepackaged foods that are required to be stable at room temperature for multiple years prior to consumption. 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 are known to have extensive health benefits. The Food Physiology study is designed to evaluate effects of providing more sources of these beneficial foods and evaluating effects on immune, microbiome, nutritional, and performance outcomes. Initial findings from a ground analog study were published in 2022. This is a first, critical element in documenting the benefits of a healthy diet as a countermeasure for astronauts.

Human history documents that exploration food system adequacy becomes central to mission success as mission length and isolation increases. NASA expects Mars missions to take up to 3 years. Resupply may not be an option, and food may even be prepositioned on Mars before crews launch from Earth. Cold storage may not be available for food, but regardless, the food system will need to be safe, nutritious, and acceptable for at least five years given the current DRMs. 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. This is not an issue for ISS, which is supported by regular resupply.

Regular resupply to ISS also enables astronauts to select 20-25% of their foods from personal preference selections, including international partner provided foods, rather than just consuming foods from the standard food system. Meal acceptability evaluations from ISS show that variety and preference are essential to prevent menu fatigue and maintain adequate dietary intake. ISS crews also have access to fresh fruits and vegetables and limited shelf-life items delivered on visiting vehicles. On exploration missions pending crew assignments or late crew changes may eliminate the opportunity for crew to select foods based on their preferences, and resource constraints may limit quantity and variety. Insufficient nutrition support, whether due to

inadequate food system content (e.g., calories, specific nutrients, bioactive compounds), nutrient degradation during storage, or inadequate intake by the crew due to factors such as menu fatigue, lack of preference, or quality degradation during storage may lead to body mass loss, muscle and bone loss, cardiovascular and immune deconditioning, and eventually nutritional deficiency(ies) that may threaten crew health and performance.

Beyond food and nutrition content and quality challenges, food resource requirements are a significant 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 overly constrained. Nutritional content, food quality, and safety must remain key requirements in any food system strategy to reduce mass and volume. On Artemis missions, mass and volume will be more limited, challenging food and water provisioning, preparation capability, and nutritional requirements. "Meal Replacement" bars have been developed to help reduce food mass and volume, but ground testing has revealed that even over short durations (less than 30 days) these have negative effects on dietary intake and morale (published in 2020). The healthiest food options – fruits and vegetables – are the least energy dense, putting them at risk for inclusion in sufficient amounts on these missions.

Studies are underway 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, infrastructure and vehicle system integration), 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.

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 in mitigating disease incidence (including cardiovascular disease, cancer, osteoporosis, muscle loss and sarcopenia, cognitive decline and dementia), traditional dietary recommendations (e.g., Dietary Reference Intakes) are simply designed to prevent deficiencies, not chronic disease. That is because much less is known about the effects of diet and nutrition on performance and disease incidence than

about how to prevent nutrient deficiency. For exploration missions outside of low-Earth orbit, we must not only stave off deficiency, we must understand how food and nutrition interact with the human system to optimize health and performance. Nutrition becomes even more important in space, where environmental factors (e.g., radiation, carbon dioxide (CO_2)), a closed environment, and stress can all affect intake and 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 may affect mood, cognitive performance and team cohesion. Optimal nutrition also improves exercise performance, maintains circadian rhythms, and promotes sleep. However, many of these outcomes have not been evaluated in relationship to either the ISS space food system, or to more restricted food systems that may be required for Moon to Mars missions. Baseline data in these areas will become increasingly important as risk trades are made between human health and vehicle systems based on resources available on future exploration missions. Ground analog studies designed to match Moon and Mars DRMs are being used to help fill this knowledge gap.

Astronauts must be adequately nourished before, during, and after missions. While preventing nutrient deficits inflight is crucial, optimizing dietary intake and nutritional status before flight 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. iPad Apps like the ISS Food Intake Tracker (ISS FIT) allow crews to easily and reliably record food consumption. This serves to provide the crew with real-time nutrition feedback, while also providing detailed information for Flight Surgeons, and also information on food use and inventory. ISS FIT can also help crewmembers select meals in preparation for specific tasks (e.g., EVAs, preparation for return to a gravitational field). The response from crewmembers was outstanding, and highlights the importance of providing tools to both enhance autonomy, and provide greater insight into actual dietary 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.

Furthermore, two key research projects, the “Nutritional Status Assessment: SMO-016E (Nutrition/SMO-016E)” and “Biochemical Profile,” yielded numerous insights, and more than 35 publications, regarding the role of nutrition in human adaptation to spaceflight. One key finding was that these experiments provided biochemical evidence for susceptibility of some (but not all) individuals to the risk of vision and ocular pathologies (aka SANS) during spaceflight. These projects 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 these same genetics, and most recently documented an association of genetics with the incidence of optic disc edema in bed rest subjects. This research highlights the need for individual assessments on the role of genetics on nutritional requirements, which may have impacts to resource limited exploration missions and could potentially have profound implications for terrestrial medicine. Countermeasures based on this line of research will be tested with ISS crews starting in 2023.

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. 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 estimated savings of more than 80 L of water *not* launched every year since 2012.

Recently, Biochem Profile data were studied to identify biochemical changes during flight which could lead to increased blood clot risk, aka, venous thromboembolism (VTE). Specifically, oral contraceptive use leads to several biochemical changes which increase VTE risk, and plausibly contributed to the recent event on ISS. These findings highlight an underappreciated risk factor for VTE: hypoalbuminemia.

Despite the successes of the Nutrition SMO and the follow-on Biochem Profile, this effort was stopped in 2018. Biochemical measures collected as part of the Standard Measures replace a few tests from the original suite of biochemical measures. As we fly more crew on missions longer than 6 months, fly more diverse crews, and test different countermeasures inflight, the need for biochemical data to help understand the implications of these differences will be critical, and represents a research gap.

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 missions was designed simply to meet cost constraints (e.g., by largely using commercially available items), and that delivered a suboptimal food system. The role for nutrition in terrestrial health and disease prevention 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 certain will be onboard exploration missions. It is HRP's goal to evaluate and define food and nutrition strategies that will optimize crew health during these exploration missions, helping to ensure mission success while imparting long-lasting benefits on crew health and performance.

4.3.2 Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance

and Health Outcomes (Short Title: Cardiovascular)

Given that exposure to the spaceflight environment can contribute to cardiovascular deconditioning, dysfunction, and remodeling, there is a possibility that astronauts will experience impaired performance and negative cardiovascular health outcomes during and after spaceflight and planetary operations. Anticipated manifestations of the cardiovascular risk outcomes depend upon design of the mission, including the magnitude and duration of exposure to altered gravity and the amount, duration, and type of radiation exposure.

During spaceflight and exploration missions, adaptations that may manifest as cardiac and vascular dysfunction could have negative health consequences as well as significantly impair crew performance and mission success. Currently, there is no clear spaceflight evidence demonstrating that the spaceflight environment is associated with increased frequency or complexity of cardiac dysrhythmias. While dysrhythmias have occurred during spaceflight, these events generally were in individuals with a history of dysrhythmias before their mission and were not considered to be clinically significant. However, factors associated with exploration missions beyond low Earth orbit may contribute to additional cardiovascular health risks such as the development of atrial fibrillation (AF). Risk factors for AF associated with long-duration spaceflight include prolonged atrial distension, increased sympathetic activation, and elevated radiation exposure contributing to higher levels of oxidative stress, inflammation, and tissue damage. Elevated levels of oxidative stress and inflammation in combination with slow or altered venous flow also may increase the risk of venous thrombosis during spaceflight. Flow stagnation and thrombus formation were observed in the left internal jugular vein in a small number of ISS astronauts (n=6 and 2, respectively, of 11 astronauts in a research cohort). Continued surveillance during International Space Station and Artemis missions, including surface operations, is necessary to characterize incidence and time course of venous flow stagnation and the risk of thrombosis during weightlessness and reduced gravity environments.

Orthostatic intolerance (OI) during re-exposure to a gravitational environment affects ~20-25% of crewmembers following ~2 week short-duration spaceflight missions and more than 60% of the crewmembers following ~4-6 month long-duration missions. Moreover, incidence of post-spaceflight OI is higher in females than males. The current suite of countermeasures to mitigate OI during re-exposure to 1-G includes in-mission exercise and end-of-mission fluid loading as well as recumbent posture, suit cooling, and lower body compression garments during re-entry and landing. Additionally, medical personnel provide ground support at the vehicle landing site and administer intravenous fluids, as needed, to mitigate blood volume loss. Signs and symptoms of OI decrease over time, but some astronauts will continue to wear lower body compression garments for several days after landing to manage OI symptoms. OI also may be a concern during exploration missions due to head-to-foot acceleration during descent to and ascent from planetary surfaces. While there were no reports of hypotension during dynamic phases of flight and during stays on the lunar surface in Apollo missions, results from subjects exposed to the spaceflight analog 6° head-down tilt bed rest suggest that some individuals, particularly females, may be susceptible to OI during accelerations <1-Gz. Investigation of the risk of OI in varying G-levels and the efficacy of compression garments in mitigating OI in females and males is ongoing.

Cardiovascular disease is considered the primary long-term health risk and concern for flight certification, particularly for long-duration missions beyond low Earth orbit. Development of cardiovascular disease terrestrially is related to several risk factors that might be exacerbated by spaceflight. Increased levels of oxidative stress and inflammation, unfavorable changes in blood lipids, and insulin insensitivity have been reported during spaceflight, although they appear to return to preflight conditions after landing. There is conflicting evidence of subclinical manifestations of cardiovascular disease in astronauts, including carotid intima-media thickening, vascular dysfunction, and increased vascular stiffness, during and immediately after spaceflight. Currently there is no clear evidence of cardiovascular structural and functional decrements from spaceflight exposure during the months and years after an astronaut's last mission, though work is ongoing to investigate the implications of mission durations up to 1 year on the International Space Station (ISS). Further, epidemiological data to date do not support an increased lifetime risk of cardiovascular death in astronauts but a recent analysis suggests that astronauts may be at an increased risk of a cardiovascular event compared to a well-matched, healthy cohort. The implications of this report are not yet clear given the small number of events in a relatively small population and few astronauts participating in long-duration (>4 months) missions have been followed for a sufficient length of time after their missions to develop clinical manifestations of cardiovascular disease.

While there is a well-established association between increased cardiovascular disease risk and moderate to high doses of radiation based on epidemiological evidence from atomic bomb survivors, radiation therapy patients, and occupationally exposed cohorts, risk of cardiovascular disease from space radiation exposure, which differs in both dose-rate and quality from terrestrial radiation, remains unclear. Further, cardiovascular disease risks resulting from interactions between altered gravity and prolonged exposures to space radiation beyond low Earth orbit are not yet well explored. The current understanding based on terrestrial exposure data suggests that the lifetime risk of cardiovascular disease is statistically greater than with normal aging for exposures only beyond 0.5 Gy-Eq (as might be experienced during a Mars planetary mission); however, cardiovascular impacts below 0.5 Gy-Eq are not well characterized. Given that radiation exposure in humans and animal models results in cardiovascular dysfunction and increased disease risk, and that extended missions beyond low Earth orbit are planned, continued monitoring of acute and long-term health is critical to estimating the cardiovascular disease risk in astronauts.

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

Astronauts perform spaceflight EVAs in confined spaces that must provide life support, nutrition, hydration, waste disposal, and consumables similar to a 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 training and in-flight task designs and concepts of operations (e.g., EVA frequency, duration, ergonomics); vehicle and habitat environmental conditions (e.g., saturation pressure, atmospheric composition of O_2 and CO_2, prebreathe); suit sizing and in-flight anthropometric changes;

crewmember muscle, aerobic, sensorimotor and cognitive fitness and performance decrements; availability of suit system and physiological sensor information (e.g., biofeedback, state and risk estimation modeling tools, decision support systems); and commercial suit design parameters (e.g., suit pressure, mass, center of gravity, joint mobility, nutrition, hydration, and waste management).

Multiple planned and ongoing research studies associated with these aspects of the EVA risk are included in the "Crew Health and Performance EVA Roadmap", which is updated periodically and currently located here: https://www.nasa.gov/sites/default/files/atoms/files/tp-20205007604.pdf. The integrated plan is intended to be program, vehicle, and suit agnostic; and includes planned and ongoing EVA tasks and projects funded by multiple organizations.

4.3.4 Risk of Decompression Sickness (Short Title: DCS)

Space exploration missions to the Moon and Mars will require frequent EVA operations to achieve mission objectives that require new prebreathe protocols, operational hardware, and atmospheric requirements. Therefore, future missions will be significantly different than Shuttle or ISS missions, and design and testing of new protocols is required to characterize variables that affect decompression sickness (DCS). 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 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. 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 are described in the "Crew Health and Performance EVA Roadmap", which is updated annually and currently located here: https://www.nasa.gov/sites/default/files/atoms/files/tp-20205007604.pdf.

4.3.5 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. A recent case study of an ISS astronaut associated persistent dermatitis with reactivation of Herpes Simplex Virus 1 (HSV1). 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. It should be noted that

more recent ISS crews have shown improvement in immune function, and reduced reactivation of viruses. This phenomenon has been attributed to several biomedical countermeasures already deployed to ISS, involving specific exercise, diet and behavioral health. Unfortunately, these countermeasures do not readily translate to deep space missions and smaller vehicles. Immune dysregulation is likely to worsen during such missions due to synergy involving 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. Although fairly well understood due to a series of ISS investigations, several other current investigations continue to characterize previously uninvestigated aspects of immunity in ISS astronauts including innate cellular function, host pathogen interactions, the impact of functional food diet as a countermeasure, DNA damage in immune cells, gene expression in leukocytes, and protein alterations. HRP continues work to 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, was published in 2019 by the same international team of authors (Makedonas et al, Frontiers, 2019). Data suggests that the immune responses of subjects who are exposed to environments that are analogous to space – including 'winterover' (one-year duration) inhabitants of research stations in Antarctica – are sufficiently similar to the in-flight phenomena that they provide a terrestrial platform in which NASA could evaluate potential countermeasures. A ground validation of the immune countermeasure referenced above was recently initiated through the National Science Foundation (NSF) at Palmer Station, Antarctica. If successful, it should be followed by a validation onboard ISS.

4.3.6 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 substantiated an increased incidence of IVD damage in astronauts that is directly related to spaceflight exposure. Further studies have attempted to characterize the effects of spaceflight on the vertebral unit (vertebral bodies/IVD/musculature), but likewise the data have not further informed the concern for IVD damage to elevate it to a risk and suggest that post-flight IVD herniation may be more associated with preflight risk factors.

4.3.7 Risk of Altered Sensorimotor/Vestibular Function Impacting Critical Mission Tasks (Short Title: Sensorimotor)

Exposure to microgravity induces adaptive central reinterpretations 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 perform operational tasks. The risk of impairment is

greatest during and soon after gravitational transitions when performance decrements may have high operational impact (e.g., control of vehicles during landing, immediate egress, and extravehicular activities following landing). These impacts are of particular concern for Lunar and Mars missions, which involve novel gravitational environments and limited surface resources. Therefore, we are currently working to characterize this risk more completely, including decrements in posture and gait, manual control, spatial orientation, motion sickness, as well as investigating spaceflight-related changes (including radiation exposure) to brain structure, which might subsequently result in changes in cognition and performance of tasks. Previous studies have established that (1) functional tasks requiring a greater demand for dynamic control of postural equilibrium showed the greatest decrement in pre to postflight performance, and (2) while there are considerable variations between crewmembers, most crewmembers experience motion sickness symptoms following long duration spaceflight. These flight and previous bed rest studies have revealed that aerobic and resistance exercise alone is not sufficient to mitigate decrements in postural stability, indicating the need for targeted countermeasures for postflight postural and gait disturbances. Early postflight sensorimotor measurements are planned through the remainder of the ISS as part of the Spaceflight Standard Measures to continue to characterize the risk as a function of flight duration and to evaluate future countermeasures. Additional inflight measures of neurovestibular adaptation are planned as part of the multidisciplinary Complement of Integrated Protocols for Human Research (CIPHER). HHC is further characterizing the risk of sensorimotor alterations for manual crew override through simulated piloting tasks following spaceflight, and motion sickness incidence and severity with early inflight and postflight questionnaires. Partial gravity parabolic flights will be used to capture dose response curves for functional task tests, ocular alignment, and manual control tasks. Characterization of crew head and body movements during landing and EVA tasks are also planned through observational measures during the early Artemis lunar sorties. Epidemiology research is also planned to investigate whether spaceflight increases fall risk during aging as a potential long-term health risk.

Research into sensorimotor risk mitigation includes both assessment of readiness to perform operational tasks as well as preflight, inflight and postflight countermeasures. Ground analogs will be validated against existing spaceflight data to develop sensorimotor assessment tools targeted for exploration missions. The feasibility of using these analog environments for preflight training will be explored in collaboration with the Flight Operations Directorate. Research to mitigate motion sickness includes both pharmaceuticals and non-pharmaceutical spatial orientation aids and incremental rehabilitation tools. Sensorimotor countermeasures designed to supplement exploration exercise to address post-landing balance and locomotor control deficits will be evaluated first during head-down bedrest and then long-duration spaceflight, including using sensory augmentation to enhance balance recovery. These countermeasures will also be implemented as self-administered integrative approaches suitable for autonomous exploration missions. HHC will also be addressing countermeasures for manual override of a lunar landing using on-orbit just-in-time training as well as spatial orientation modeling to predict when disorientation poses greatest risk for abort/override decisions and recommend when active countermeasures like sensory cueing would be most beneficial.

4.3.8 Risk of Impaired Performance Due to Reduced Muscle Size, Strength and

Endurance (Short Title: Muscle) and Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity (Short Title: Aerobic)

Prolonged exposure to spaceflight results in deconditioning of major organ systems such as decreased cardiac and sensorimotor function, reduced bone mineral density, and the loss of skeletal muscle mass and strength. This deconditioning leads to decrements in muscle strength and endurance, fatigue resistance, motor performance, and connective tissue integrity that ultimately affect the maximal capacity of aerobic and skeletal muscle strength that further affect submaximal physical work capacity. NASA's vision for future exploration missions depends on the ability to protect against deconditioning. Astronauts must maintain health, safety and performance of EVA, in both 0-G and during ambulation in partial gravity, and to allow astronauts to safely egress from vehicles in a variety of landing scenarios, including water landing upon return to Earth and undefined planetary/lunar landings. The amount of deconditioning and the time required to recover from microgravity exposure will influence the astronauts' ability to complete physically demanding tasks during an exploration mission, including habitat construction and EVA, especially when the astronaut must work against a semi-rigid pressurized suit during EVA for up to 8 hours.

For 6-month ISS missions, crew launch must have access to effective and robust exercise countermeasure systems, and adhere to exercise countermeasures as prescribed in-flight, so that they can maintain or return above the task standard for aerobic fitness and muscle strength. Astronauts perform daily aerobic and resistance exercise during ISS missions to maintain physical fitness; however, to date these exercise countermeasures have not been fully protective. Briefly, maximal aerobic capacity (VO_2pk), lower body muscle cross-sectional area and strength are decreased by approximately 10% to 15% after short-duration (~14 days) and long-duration (~6 months) ISS spaceflight and simulated microgravity exposure (i.e., bed rest). Since installment of the Advanced Resistance Exercise Device (ARED) on ISS in 2009, pre to post-flight reductions in knee extension and flexion strength are 7% and 12.5%, respectively, average ankle flexion and extension strength losses are ~12%. Importantly, there is considerable variability among crewmembers with respect to post-flight changes in fitness, with some crewmembers experiencing no or minimal losses and others with 30% decrements in VO_2pk or muscle strength. It is currently unknown why this occurs and the large individual variabilities suggest differences in either genetics, preflight fitness levels, and individuals exercise prescriptions and equipment countermeasures need further careful evaluations. Efforts should be made to try to understand the current status of pre-flight, in-flight and post-flight exercise performance capability and what the goals/target areas for protection are with the current in-flight exercise program. Physical fitness outcomes have been acceptable according to current expectations for crewmember performance on return to Earth, however, there still is large variability of fitness from pre to post spaceflight that can be improved upon. Moreover, for missions to the Moon, establishment of a lunar base, and interplanetary travel to Mars, the functional requirements for human performance during each specific phase of these missions have not been sufficiently characterized and the development of effective countermeasures or current standards are adequate to meet physical performance requirements. Muscle strength and aerobic fitness standard updates have been proposed for 0g EVA and vehicle egress. Additional data collection and funding is required to develop partial gravity EVA standards. These standards

will provide information necessary for programs to develop requirements for systems and hardware (e.g., spacesuits, Environmental Control and Life Support System (ECLSS), exercise hardware) needed to maintain these performance capabilities. Maintenance of VO2peak and strength may prove to be even more difficult during exploration missions where exercise equipment will be limited in volume and power capabilities and communication to the astronauts will likely be delayed and less frequent.

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

Ocular structural and functional changes have been observed in crewmembers who participated in long-duration space missions and NASA has termed the risk of developing these *Spaceflight Associated Neuro-ocular Syndrome (SANS)*. Previously optic disc edema was reported only when fundoscopy images demonstrated edema of Frisen grade ≥ 1, which has been observed in 13% of crew flying long-duration ISS missions. Recently optical coherence tomography (OCT) images that provide objective measures of edema based on a change in total retinal thickness (TRT), revealed approximately 67% of crew demonstrated the earliest signs of edema (ΔTRT ≥ 20µm) which are likely sub-clinical. Combine with signs of retinal and/or choroidal folds (21%), globe flattening observed on magnetic resonance images (MRI) at the optic nerve head (21%), and/or changes in refractive error ≥0.75D (15%), 70% of crewmembers demonstrate at least one SANS finding. Not all of these findings develop in affected crewmembers. While these ocular findings were not observed during short-duration missions (14 days) the prevalence and/or magnitude of these findings during 6-month missions and possible progression during 1-year missions suggests that longer duration missions may play a role in the development of SANS findings. 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 veins and increased resistance in outflow from the eye veins, chronic mild elevation of intracranial pressure, localized elevation of cerebrospinal fluid pressure within the sheath of the orbital optic nerve, and impaired drainage in the cephalad lymphatic and/or glymphatic systems, and there is a possibility that some of these factors may be augmented due to individual susceptibility and genetic variability. The goals of several ongoing and future research studies are 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.

4.3.10 Risk of Adverse Health Effects Due to Host-Microorganism Interactions (Short

Title: Microhost)

While current preventative measures limit the presence of many 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, concentration, and diversity. 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 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.

4.3.11 Risk of Reduced Crew Health and Performance Due to Hypoxia (Short Title: 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.

With the 8.2 psia and 34% O_2 becoming 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 plan to 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.

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

Spaceflight-induced bone changes are largely targeted to regions of the skeleton that experience larger reductions in mechanical loading in microgravity, i.e., weight-bearing sites on Earth. Hence, these skeletal sites may be more at risk for fracture during mission operations. The risk for fracture associated with falls is minimal during missions in microgravity because impact loads are extremely low. In contrast, applied loads to bone will increase in the gravitational environment of celestial bodies and with the performance of mission activities during surface exploration, 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, suggests that mechanical loads to bone during a fall on the Moon or Mars are unlikely to lead to fracture. As a result, there is no active research regarding spaceflight clinical fracture management at this time as the risk is considered "accepted" for all Design Reference Missions. However, there is still ongoing research to further characterize skeletal changes beyond the measurement of areal bone mineral density (BMD) following long-duration missions. The recent association of increased hip and spine fracture counts following astronaut exposure to a long-duration spaceflight will enable the updating of computational models and influence countermeasures used during or after future exploration missions.

4.4 Space Radiation

4.4.1 Risk of Radiation Carcinogenesis (Short Title: Carcinogenesis)

One of the many environmental hazards in space flight is exposure to chronic, low dose-rate high energy particles that make up the space radiation environment. These exposures increase the likelihood of cancer morbidity and mortality to crew over their lifetimes. Due to lack of resource availability and constraints in spacecraft design, shielding crew from the high energy particles that comprise the space radiation environment (87% protons, 12% helium, 1% higher charge and energy [HZE] ions) remains imperfect, leaving crew members exposed to the space radiation field, particularly during deep space and interplanetary missions. While operational risk assessment for the astronaut population is currently limited to estimates of excess cancer mortality, to mitigate the risk of radiation carcinogenesis, the Space Radiation Element has implemented a robust research strategy to reduce the risk of both astronaut mortality and morbidity from cancer.

Ground-based analog studies conducted at the NASA Space Radiation Laboratory (NSRL) are used to better characterize the role of radiation quality and dose-rate in space radiation-induced carcinogenesis using monoenergetic single ion beams, as well as various GCR simulation beams that approximate the local space radiation environment encountered inside a spacecraft during space flight. The information gained through these ongoing and future ground-based studies will help to characterize the carcinogenic risk from space radiation exposures, inform uncertainties in risk estimates, and develop tactical mitigation strategies.

The initiation and implementation of the NASA Specialized Center of Research (NSCOR) tasked groups to characterize different mechanisms of radiation carcinogenesis specific to the tissue types hypothesized to be major contributors to overall cancer risk including lung, breast, colon, the blood and lymphatic system (leukemia and lymphoma), liver, and brain. These efforts have led to the development of tissue-specific research models to support the identification of tissue-specific risk factors as well as contribute necessary information to aid in the early detection of pre-malignant disease and health monitoring through the identification of biomarkers.

New, data-driven computational models are under investigation to assess radiation carcinogenesis risk and translate ground-based radiation research results to astronauts. The baseline NASA radiation carcinogenesis risk model is primarily based on human epidemiological data from the Life Span Study of atomic bomb survivors (LSS). Other radiation exposed cohorts, including the collection of radiation worker cohorts that make up the Million Person Study (MPS), are being assessed for potential incorporation into risk models to estimate the risk of radiogenic cancers arising from exposures like the astronaut population. To test risk model assumptions (including transfer of risk across populations, use of average incidence and mortality rates for the U.S. population, role of attained age and age at exposure, and radiation quality and dose-rate effects) past, current, and future data will be assessed using advanced biostatistical and computational methods. Further, to more fully understand the uncertainties surrounding assessment of radiation carcinogenesis risk, ensemble modeling approaches are being explored.

Advances in terrestrial cancer early detection and treatment modalities will continue to be monitored and supported where appropriate. Collaborative committees with federal and state agencies (NCI, NIAID, CPRIT) and cancer related professional societies (American Association for Cancer Research, American Society of Therapeutic Radiation Oncology, Radiation Research Society, etc.), and other stakeholders will monitor advancements in early detection and treatment outcomes. These advances will be utilized to inform clinical best practices for monitoring astronaut health during their career and into retirement. Interagency collaboration will also help develop infrastructure to support identification and validation of medical countermeasures to reduce carcinogenesis risk in appropriate biological models.

The Space Radiation Element will continue to sponsor studies utilizing a systems biology approach to provide a framework to integrate mechanistic studies of cancer risk across multiple levels of understanding (molecular, cellular, tissue, systems, and organismal levels). Emerging bioinformatics data sets (transcriptomics, genome sequencing, etc.), and the establishment of tissue archives will provide resources for future analysis to answer specific questions in a timely fashion. Tech watches will also be implemented to explore new approaches in terrestrial cancer research and model development to leverage the broader field of cancer research to support tissue-specific risk assessment.

Specific goals, deliverables, and recommended targets for closure efforts are outlined in the Cancer Gaps and questions can be directed to the Space Radiation Element Scientist, Deputy Element Scientist, and Discipline Leads.

5 CONTENT IN THE HUMAN RESEARCH ROADMAP

The IRP contains detailed research plan information in a standard format, including a graphical depiction via Risk Approach Plan 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, state of knowledge, and mitigation strategy, as detailed below. A risk rating for DRMs, a link to the Risk Approach Plan 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.
- HRP Risk Status: this field provides information on the current status of the risk (or concern) from the HRP perspective.
- 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.
- HSRB State of Knowledge: this is the HSRB-approved State of Knowledge for each risk. This section highlights selected evidence that supports the current Risk Posture and frames it as an interpretation of what is known in the larger evidence base about that Risk. Evidence from various types of data - spaceflight data, terrestrial data, analog data, mechanistic studies and models, anecdotal information and subject matter expert input – is presented at a high level.
- 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 Approach Plan chart, which shows the forecasted timeline of high-level risk milestones and a strategic flow of the research logic for improving risk ratings, is accessed through the Risk Approach Plan tab on each risk page. Some RAP charts are in development. The RAP Chart Overview, seen in Section 6, shows an example of the chart. Specific highlighted risk milestones shown in the top bar represent thresholds in movements of the risk ratings (e.g., red to yellow to green).

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 status of the gap; 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 MDRP, or gaps across multiple risks or MDRPs. 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 Table 1 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.

5.4 MDRP Page

Each HRR MDRP has a page with relevant information, including short title, responsible entity, and research approach. The risks integrated in the MDRP and a listing of the gap(s) relevant to the specific MDRP are also included on each MDRP page.

TABLE 1. CATEGORY OPTIONS FOR DELIVERABLES

Category	Subcategory	Example Deliverables
Requirement	Vehicle/Habitat	HSIA Design and inputs to system design including initial JIT training & Standards
	Vehicle/Habitat Interface	LoC IV Concept of Operations, Accepted Medical Condition List, System Model
	Guidelines/criteria	Development of a HSIA Failure Recovery process; Team Composition Algorithm Validated
Technology or Tool	Systems Solutions, Prototype Hardware or Software	Mars Adaptive Training-Integrative Knowledge System (MATRIKS) - Leverage from onboard in-situ performance to drive contextual training program; Informing Mission Planning via Analysis of Complex Tradespaces (IMPACT) tool
	Computational Models or simulations	MERA Anchor Model
	Informatics	Biomarker thresholds (ground validation) linked to performance
Countermeasure	Clinical Procedure or Prescription	Clinical Guideline on Decision Thresholds: Operational performance metrics, standard measures
	Protocol	Clinical Guideline :Biomarker thresholds linked to performance (flight)
	Prototype Hardware or Software	Test integration of onboard sensors and HSIA response processes
Standard	Update	CO_2 standard
	New	CVD PEL
Risk Characterization, Quantification	Evidence	Effects of Transdermal Vagal Nerve Stimulation (tVNS) on Cognitive Performance Under Sleep Deprivation Stress
Study Results	Customer Requested Study or Analysis	TBD

Requirement or Guideline

The “Requirement” deliverable is chosen when the deliverable provides information that is relevant to a higher-level standard or requirement (or requirements set) owned by another Program. 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 System Requirements Review (SRR) or Preliminary Design Review (PDR) 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

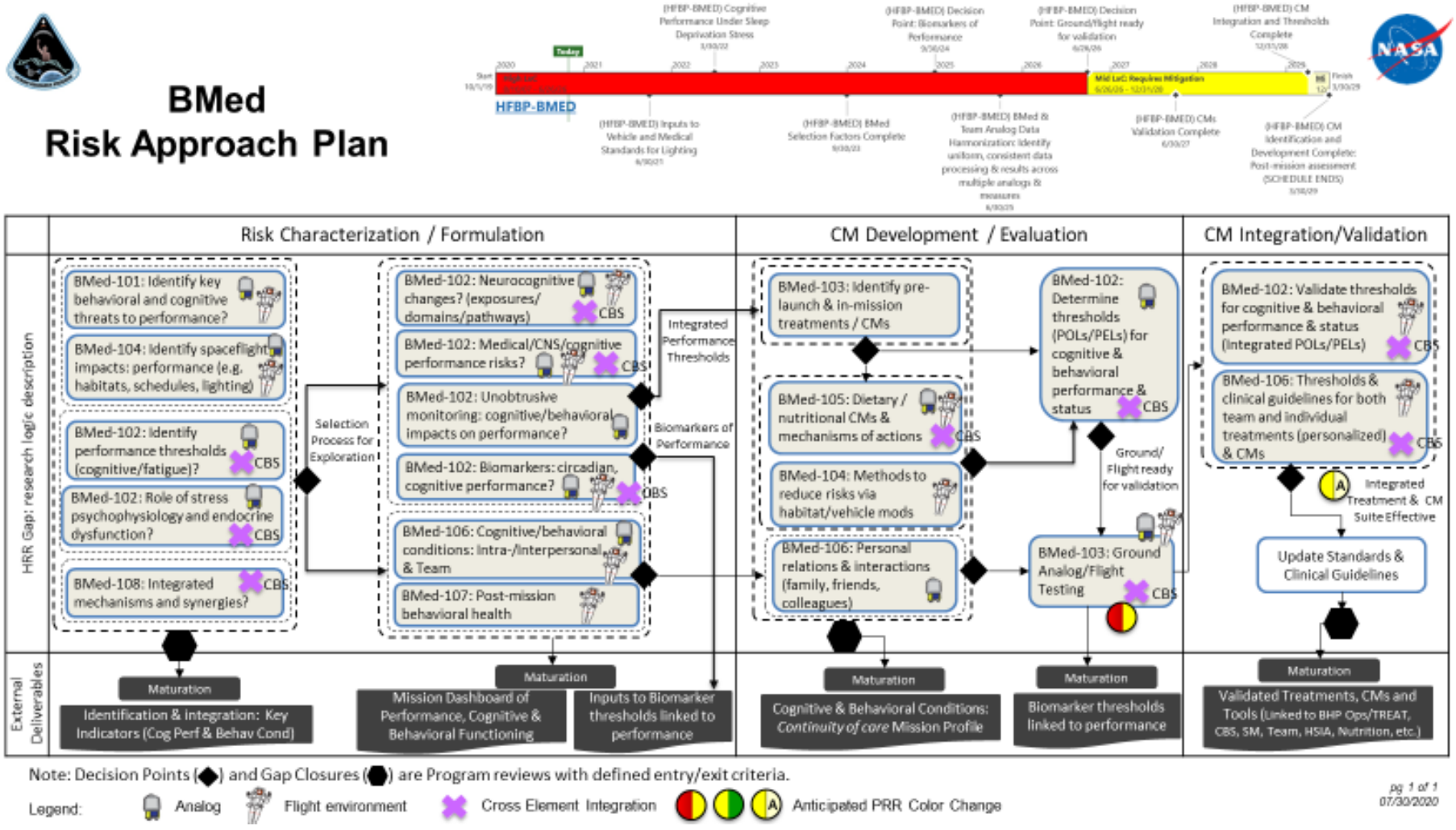
impacts the rating of the likelihood or consequence of a risk. It is also applied when the results of the study are anticipated by the space medical operations community.

Study Results

A study or analysis is requested by an HRP customer. 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 RISK APPROACH PLAN (RAP) CHART

RAP Chart Example (*notional data*): Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (BMed)



APPENDIX A - LINK TO HUMAN RESEARCH ROADMAP

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

https://humanresearchroadmap.nasa.gov/

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

AF	atrial fibrillation
AI	artificial intelligence
ARED	Advanced Resistance Exercise Device
ATD	anthropomorphic test devices

B

BEO	beyond Earth orbit
BMD	bone mineral density
BMed	behavioral medicine

C

CBS	Combined Behavioral Stressors
CDR	Critical Design Review
CHAPEA	Crew Health and Performance Exploration Analog
CHMO	Chief Health and Medical Officer
CHP	Crew Health and Performance
CHS	Crew Health & Safety
CIPHER	Complement of Integrated Protocols for Human Research
CMO	Chief Medical Officer
CNS	central nervous system
CO_2	carbon dioxide
CPRIT	Cancer Prevention and Research Institute of Texas
CR	Change Request
CRL	Countermeasure Readiness Level
CSA	Customer-Supplier Agreement
CV	cardiovascular
CVD	cardiovascular disease

D

DAG	Directed Acyclic Graph
DCS	decompression sickness
DNA	deoxyribonucleic acid
DRM	Design Reference Mission

E

EIMO	Earth Independent Medical Operations
EVA	Extravehicular Activity
ExMC	Exploration Medical Capability

F

G

G	gravity
GCR	galactic cosmic rays

H

H_2O	water
HERA	Human Exploration Research Analog
HFBP	Human Factors and Behavioral Performance
HHC	Human Health Countermeasures
HHPD	Human Health and Performance Directorate
HIDH	Human Integration Design Handbook
HMTA	Health and Medical Technical Authority
HRP	Human Research Program
HRPCB	Human Research Program Control Board
HRR	Human Research Roadmap
HSI	human systems integration
HSIA	Human Systems Integration Architecture
HSID	Human Systems Integration and Design
HSRB	Human System Risk Board
HSV1	Herpes Simplex Virus 1
HZE	high charge and energy

I

IMPACT	Informing Mission Planning via Analysis of Complex Tradespaces
iPRR	integrated Path to Risk Reduction
IRP	Integrated Research Plan
ISS	International Space Station
ISS FIT	ISS Food Intake Tracker
ISS UPA	ISS Urine Processor Assembly
IVD	intervertebral disc

J

JIT	just-in-time
JSC	Johnson Space Center

K

L

LDEM	long duration exploration mission
LEO	low Earth orbit
LHIC	Lead HMTA Integration Center
LoC	level of care
LOC	Loss of Crew

LSDA	Life Sciences Data Archive
LSS	Life Span Study
LxC	Likelihood and Consequence

M

MATRIKS	Mars Adaptive Training-Integrative Knowledge System
MCC	Mission Control Center
MDRP	Multi-Disciplinary Research Plan
MERA	Multi-model Ensemble Risk Assessment
MPS	Million Person Study
MRI	magnetic resonance images
MRID	Medical Requirements Integration Document

N

NASA	National Aeronautics and Space Administration
NCI	National Cancer Institute
NCRP	National Council on Radiation Protection
NHV	net habitable volume
NIAID	National Institute of Allergy and Infectious Diseases
NRA	NASA Research Announcement
NSCOR	NASA Specialized Center of Research
NSF	National Science Foundation
NSRL	NASA Space Radiation Laboratory

O

O_2	oxygen
OCHMO	Office of the Chief Health and Medical Officer
OCT	optical coherence tomography
OI	orthostatic intolerance

P

PDR	Preliminary Design Review
PEL	permissible exposure limit
PI	principal investigator
P_IO_2	partial pressure of O_2
POL	performance outcome levels
PRD	Program Requirements Document
PRR	Path to Risk Reduction

Q

R

R&TD	research and technology development
RAP	Risk Approach Plan
REV.	Revision
RFP	Request for Proposal
RID	Review Item Discrepancy
ROI	Research Operations and Integration

S

SANS	spaceflight associated neuro-ocular syndrome
SBIR	Small Business Innovation Research
SCLT	System Capability Leadership Team
SMO	Supplemental Medical Objective
SOMD	Space Operations Mission Directorate
SR	Space Radiation
SRR	System Requirements Review
STD	Standard

T

TBD	to be determined
TRISH	Translational Research Institute for Space Health
TRL	Technology Readiness Level
TRT	total retinal thickness

U

UPCG	Unique Processes, Criteria, and Guidelines
USOS	US Orbital Segment

V

VTE	venous thromboembolism

WXYZ