JSC 66705

Human System Risk Management Plan

Human Health and Performance Directorate

JSC Health and Medical Technical Authority

Revision A

October 2020

~~National~~ Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

NASA APPROVAL SHEET
Human System Risk Management Plan
JSC Health and Medical Technical Authority

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CHANGE HISTORY

REVISION/ CHANGE	DATE	AUTHORIZATION	DESCRIPTION OF CHANGE
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Revision A	10/01/2020	SA-02403	Complete Revision

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1.0 INTRODUCTION

Risk is technically defined as the probability and magnitude of a loss, disaster, or undesirable event.

Risk Management is defined as the identification, assessment, and prioritization of risks followed by coordinated and economical application of resources to monitor, minimize, and control the probability and/or impact of undesirable events.

Human System Risks are a special category of risks that National Aeronautics and Space Administration (NASA), as an Agency, has to contend with when engaging with the challenges of human spaceflight. While programmatic and institutional safety risks are often tied to a specific program or activity, Human System Risks are designed to inform NASA Technical Standards, to protect human crews independent of any specific spaceflight program. The term 'Human System Risk' is often interchangeably used with the term 'Risk' in the Human Health and Performance Directorate (HHPD) community. For the purposes of this document we will refer to Human System Risks as the ~30 configuration managed risks that the Human System Risk Board (HSRB) tracks. Probability and Magnitude are referred to in this document as Likelihood and Consequence for the purposes of consistency with other NASA risk management documentation.

A **Human System Risk** is a recognized potential undesired flight crew health or performance outcome that has a clear consequence and attendant likelihood supported by evidence for a given Design Reference Mission (DRM) category. The HSRB uses DRM categories to assess Human System Risk against proposed NASA missions, loosely defined by destination, operating environment, and expected duration in lieu of constantly changing proposed missions. Due to the small number of humans that have flown in space, significant lack of knowledge and uncertainty remain surrounding how exposure to the spaceflight environment changes human health. These changes can impact an astronaut's ability to perform critical tasks tied to mission objectives while in mission, as well as impact their ability to be recertified for flight status after spaceflight missions. Human System Risks are the only risks that also address the long-term health effects of the spaceflight environment on crew beyond the end of a program. An understanding of the short -term and long -term effects of the spaceflight environment on humans is still evolving. In the case of this document, it is useful to define health and performance for the purposes of understanding risk. Health in this case refers to the absence of medical conditions that are likely to harm or cause decrements in performance needed to achieve mission objectives. Performance refers to the individual crewmembers ability to successfully complete tasks asked of them in the course of a mission. Medical conditions or health decrements can contribute to performance decrements.

The goal of Human System Risk management is to articulate and track Human System Risks to ensure that the knowledge gained through human spaceflight and complementary advances in applicable terrestrial medicine and human performance are captured, documented, and applied in evolving human spaceflight programs to reduce the risks that crews will face in exploration spaceflight both today and for the foreseeable missions of the future.

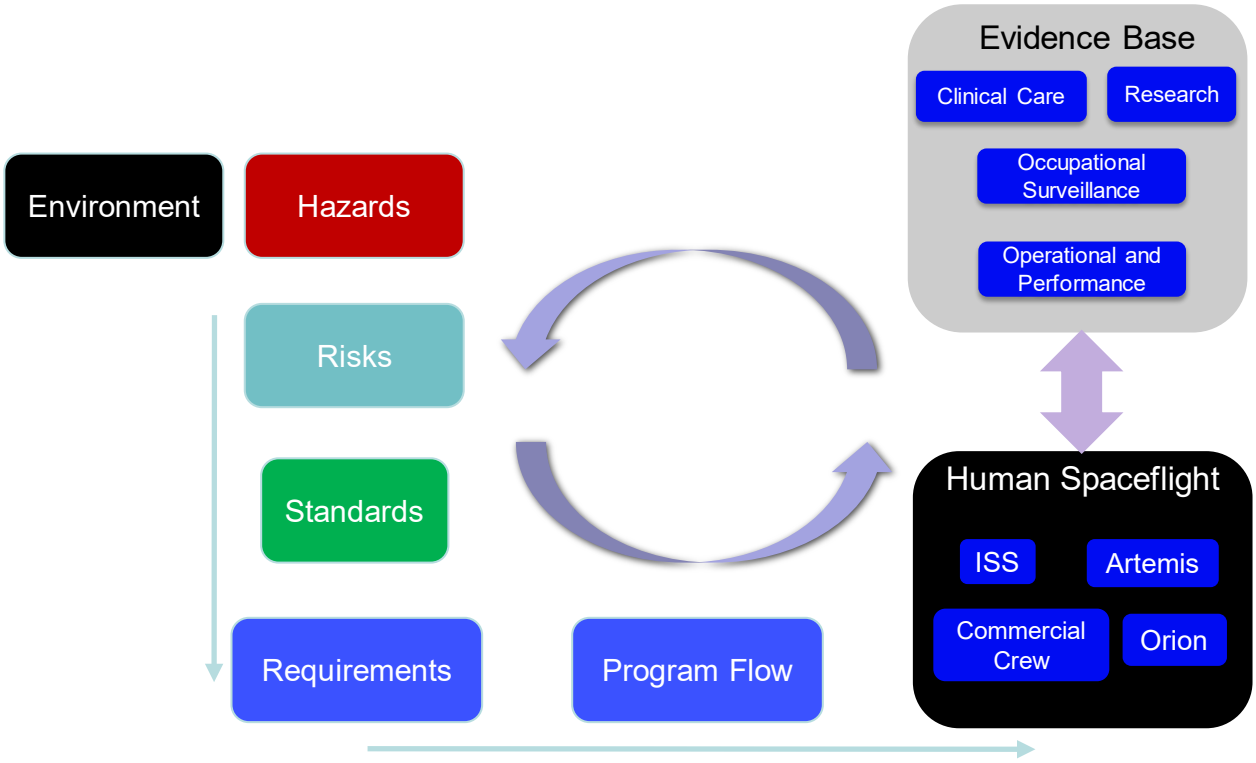

Figure 1: Evolution of Human System Risks in Human Spaceflight

Figure 1 shows the process for risk insight and management at a high level (items represented in the figure above are listed in italics). Crews are subjected to the unchangeable aspects of the space *environment* in spaceflight. This environment is characterized by *hazards* which are unchangeable aspects of spaceflight harmful to humans.

Five main hazards have been identified:

1. Altered gravity – Exposure to a gravity environment that is less than Earth-normal begins a process of adaptation; some of these adaptations create issues for human bodies that developed to function in a 1G (gravity) environment.
2. Radiation – Risk exposure damages biological cells in duration- and intensity-dependent manner and may lead to clinical illness or contribute to human performance decrements.
3. Isolation and Confinement – Increasing time in isolation increases the risk of psychological, physical, and mental health issues for crew.
4. Hostile closed environment – The habitable volume and environmental systems required to enable life and work in any space vehicle or habitat can expose astronauts to different atmospheric, water, or microbial challenges as well as acceleration environments that can lead to injury.
5. Distance from Earth – Impacts real-time communications, consumables resupply, time to evacuation, and available mass and volume that can limit inclusion of countermeasures.

From these hazards, specific Human System *Risks* are identified that capture the likelihood and consequence of challenges to the human system experienced in the spaceflight environment. These Risks highlight the human's capabilities and needs that, when considered in a consistent, methodical fashion, must be recognized, assessed, and either mitigated or accepted. One major pathway for mitigating risks is to use the prior evidence and experience base from human spaceflight to either develop new appropriate *standards* or refine/update existing standards that capture the lessons learned. Those standards are held by the Office of the Chief Health and Medical Officer (OCHMO) and levied as *requirements* where appropriate when new programs are set up by the Agency. Human space flight requirements are managed through programmatics as described in NASA Procedural Requirements (NPR) 7120.5, and are dispositioned with appropriate data and rationale in order to certify design and demonstrate flight readiness. Once *human spaceflight* is underway in a program, tracking the response of the human system to the environment and the vehicle systems is critical to updating the *evidence base* which captures crew health and performance data from clinical care, research, occupational surveillance and operational performance data sources. As human spaceflight is still a relatively new endeavor, performing the appropriate surveillance and research to characterize the human response in space ensures we are learning from each mission what our actual Risk Posture is and how we can mitigate or accept Human System Risks. The **Risk Posture**, or the agreed upon understanding of a Human System Risk decided on by HSRB, enables the HSRB to communicate the likelihood, consequence and risk disposition that the agency and crew are likely to carry for a given Human System Risk based on the best available evidence. This activity allows us to apply those lessons intelligently to future spaceflight programs.

The management of these Human System Risks is mandated by NPR 7120.11 NASA Health and Medical Technical Authority (HMTA) Implementation and governed by an integrated framework of Risk Informed Decision Making (RIDM) and Continuous Risk Management (CRM) mandated by NASA and described in NPR 8000.4 NASA Procedural Requirements. These are intended to inform decision making through better utilization of risk information and proactive risk management. As prescribed by NPR 8000.4, when a threat is identified or when a potential failure to meet the required criteria has been identified, the risk management process is initiated using the following RIDM steps:

1. Identify decision alternatives: consider challenges and opportunities based on stated objectives.
2. Analyze alternatives: apply subject matter expertise across disciplines to bound the likelihood of occurrence or lessen the negative impact of key drivers and impacts on objectives criteria.
3. Plan an option: after a deliberative review informed by risk analysis results, select a decision alternative, document the performance measure values that informed its selection, and define the baseline objectives criteria for CRM.

This process applies well to programmatic risks but is more difficult to implement in Human System Risks. The nature of Human System Risks is such that the Agency and crews carry risks beyond the immediate spaceflight program or mission at hand. These Risks span across multiple programs in both current and future spaceflight; compounding this, multiple programs may contribute to a single mission. For this reason, we use DRMs as well as risk impact categories of In-Mission Risk, Long Term Health Effects, and Crew Flight Recertification status to capture the full spectrum of risks that human crews face

in spaceflight. This approach is particularly useful when a threat entails high stakes, complexity, uncertainty, multiple attributes or competing objectives, or a diverse range of stakeholders. It also improves deliberation during consideration of the crew health and performance requirements through use of the program's experience base and tacit knowledge.

The HSRB has the overall responsibility of tracking the evolution of Human System Risks, maintaining a consistent, integrated risk management process to mitigate those risks, and to develop the Risk Posture for relevant DRMs. This document captures the process to ensure timely identification of Human System Risks and to identify processes for acceptance of the Human System Risk and accountability that are clear, transparent, and definitive using CRM principles.

1.1 PURPOSE OF THE DOCUMENT

This Human System Risk Management Plan (JSC-66705) describes the guidelines for performing practical risk management as executed by the HSRB on behalf of the HMTA, and overseen by the HSRB Risk Management Office. This document defines the processes concerning the identification, assessment, status reporting, coordination, integration, and mitigation of all Human System Risks pertaining to flight crew health (including occupational surveillance) and performance for space missions. It provides the approach that supports HSRB's required decision making as described in the Human System Risk Board Charter (SA-CHT-002). This plan shall be reviewed and updated, as required, to reflect changes and improvements to the process.

1.2 SCOPE AND APPLICABILITY OF DOCUMENT

This document is applicable to the Human System Risks pertaining to flight crew health and performance for space missions within pre-, in-, and post-flight timeframes. Institutional and human space flight program or project level risks are addressed through other risk processes captured in their respective risk management plans. This document does not address the disposition of programmatic risks (e.g., schedule, budget) that are not directly tied to human health and performance concerns, or in the disposition of hardware or software development risks specific to flight programs.

1.3 RELATED DOCUMENTS

Document No.	**Title**
JPR 7120.8	*Lyndon B. Johnson Space Center Health and Medical Technical Authority Implementation*
JSC 28330	*Configuration Management Plan – Human Health and Performance Directorate*
JSC 66377	*JSC Health and Medical Technical Authority Transition to Operations Process*
NASA-STD-3001	*NASA Space Flight Human System Standard*
NID 1600.55	*Sensitive But Unclassified (SBU) Controlled*

Document No.	Title
	Information
NPR 1000.3	*The NASA Organization*
NPR 7120.11	*NASA Health and Medical Technical Authority (HMTA) Implementation*
NPR 7120.5	*NASA Space Flight Program and Project Management Requirements*
NPR 8000.4	*Agency Risk Management Procedural Requirements*
NPR 8705.2	*Human-Rating Requirements for Space Systems*
NPR 8900.1	*NASA Health and Medical Requirements for Human Space Exploration*
SA-CHT-002	*Human System Risk Board (HSRB) Charter*
SA-HDBK-001	*Don't Panic: A Risk Custodian's Handbook for the Human System Risk Board*

1.4 RISK MANAGEMENT APPROACH

The approach used for managing the Human System Risks is based on the principles of CRM that establish the process for the identification of Human System Risks and Concerns, the evaluation and approval of the evidence-based risk assessments, the endorsement of cross-program and multidisciplinary plans, the determination of Risk Disposition, and the tracking, documentation and communication of risk information and activities. The process is proactive in nature and structured to provide early insight through appropriate collection and use of data in order to establish the appropriate Risk Posture for the Human System Risks and manage their reduction. The description of the adaptation of the CRM framework into the Human System Risk process is provided in Section 3.0.

The purpose of the HSRB is to enable the translation of evolving information and evidence to inform our understanding of Risk Posture that crews face in spaceflight and to improve that Risk Posture. The HSRB accomplishes this through:

1. Management of all Human System Risks pertaining to flight crew health and performance for space missions, which includes pre, post, and in-flight risks.
2. Providing a forum to discuss, integrate and update the most current evidence-based understanding of Human System Risks and Risk Posture for specific Design Reference Missions (DRMs).
3. Providing a forum for the Human Health and Performance Directorate (HHPD) to consider and respond to Risk Posture determinations.

The HSRB implements and maintains a consistent, integrated process for managing Human System Risks. It establishes evidence-based Risk Posture assessments and makes recommendations to the Chief Health

and Medical Officer (CHMO), Standards Manager, and programs to support risk-informed decisions. The HSRB interfaces with the Human Health and Performance Control Board (HHPCB) to address the application of risks to specific flight program needs. The flight program and project managers work with HMTA in the development, review, and concurrence of program level human system requirements in order to meet the NASA Standards as stipulated in NASA Health and Medical Technical Authority (HMTA) Implementation (NPR 7120.11). HSRB assesses Human System Risks against DRMs while the HHPCB is responsible for official HMTA positions and recommendations to flight programs.

2.0 ORGANIZATIONAL CONTEXT AND STAKEHOLDERS

The organizational context within which Human System Risks are managed at NASA is shown in Figure 2. The Human Exploration and Operations Mission Directorate (HEOMD) at NASA Headquarters is the funding authority for the Crew Health and Safety (CHS) and the Human Research Program (HRP), primary program stakeholders of the HSRB whose respective control boards serve as the information forums for significant decisions. The authority of the HSRB derives from the Office of the Chief Health and Medical Officer (OCHMO) responsibilities delegated by the CHMO to the Johnson Space Center (JSC) Chief Medical Officer (CMO) in support of JSC HMTA functions stipulated in the NPR 7120.11 and *Lyndon B. Johnson Space Center Health and Medical Technical Authority Implementation* (JPR 7120.8). The HHPCB of the HHPD and the HSRB are both Level 2 boards for the HMTA and they also serve HHPD functions as well. The HHPCB focuses on program risks for current and near term human spaceflight programs as well as institutional risks and the HSRB focuses on Human System Risks as applied to the breadth of expected human spaceflight programs.

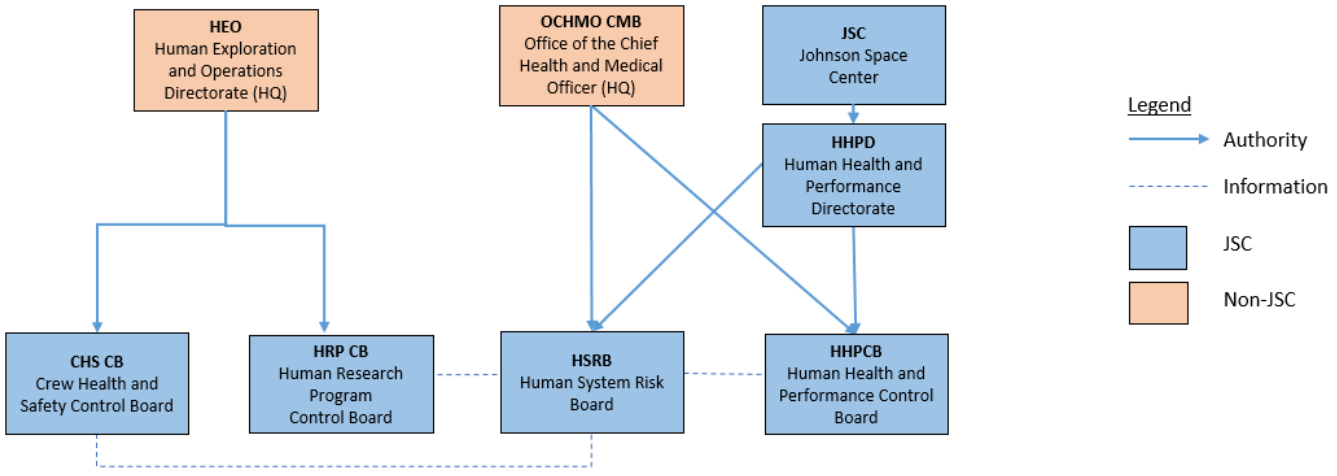

Figure 2: Organizational Context Supporting Human System Risk Management Process

The following section identifies the primary stakeholders and relevant organizations that are

instrumental in the execution of Human System Risk management.

2.1 HUMAN SYSTEM RISK BOARD (HSRB)

The HSRB is the HMTA board for the management of all Human System Risks pertaining to flight crew health and performance for space missions, which includes pre-, post-, and in mission risks. It has the overall responsibility to implement and maintain a consistent, integrated risk management process and provides a forum to discuss, integrate and update the most current evidence-based understanding of Human System Risks and Risk Posture for specific DRMs and for the HHPD to consider and respond to Risk Posture determinations. The Board is chaired by the HMTA Delegate to Human Spaceflight Risk Reduction Management (also the HHPD Assistant Director for Human System Risk Management) with the JSC CMO as the alternate chair.

HSRB decisions and recommendations are used to guide the medical, scientific, and technology development activities associated with controlling these Risks. The HSRB Board Chair receives inputs and recommendations from the board members on decisions that need to be made and he/she has the ultimate authority over final decisions. The day-to-day execution of these risk reduction activities is assigned to other entities, such as the funding programs, that determine how mitigation plans will be implemented and the amount of funding to be committed. These funding entities include programs (e.g., International Space Station (ISS), HRP, CHS, and the Commercial Crew Program (CCP)) and non-programs (e.g., Habitation Crew Health and Performance Systems Capability Leadership Team (Habitation - CHP SCLT); a risk may have multiple funding entities contributing to risk reduction.

Within the risk process, the HSRB establishes official HMTA positions on Risk Posture. For decisions that are risk neutral or that improve the Risk Posture, HSRB reports them to the CHMO for awareness at its quarterly reporting updates. For decisions that accept more risk on behalf of the government or which represent significant changes to red or critical risks, the HSRB brings them forward to the CHMO for concurrence. These positions are the agreed upon understanding of the level of risk the Agency and crew are likely to carry for a given risk scenario, for a given DRM, based on the best available evidence. The HSRB also approves of or disapproves of proposed risk mitigation plans brought forward by stakeholders. Risk mitigation plan packages should include a high level overview of the strategy for either characterizing or creating countermeasures for the Risk, deliverables expected to facilitate Risk reduction, and a rough schedule for delivery of those deliverables. Deliverables can include knowledge products, countermeasures, standards and requirements recommendations. The Board ensures that risk disposition and knowledge of the Human System Risks are adequately disseminated to stakeholders.

The Human System Risk Board Charter (SA-CHT-002) contains the detailed roles and responsibilities of Board members and Board support personnel/teams.

2.1.1 Human System Risk Board Risk Management Office

The HSRB Risk Management Office is the primary office that governs the execution of the Human System Risk management process in support of the HSRB. It is led by the HSRB Chair, who is also referred to as

the Risk Manager. The Risk Manager is supported by at least one Risk Integrator who provides technical and logistical assistance for the implementation of the risk process and management tools including the planning for Board meetings. A Configuration Management (CM) Specialist facilitates the CM process that supports meeting minutes development, risk record archival and updates, and the management of the HSRB Dashboard, a central repository of the actions, minutes and presentations. The current repository is housed on the HHPD SharePoint.

2.1.2 Risk Custodian Team

Risk Custodians are individuals assigned by the HSRB Chair in coordination with HHPD Divisions to coordinate activities throughout the risk management process for a particular Human System Risk. There are two Risk Custodians assigned to each Risk that represent the operational and research perspectives of risk mitigation. They work together to coordinate content development among relevant risk stakeholders. Additionally, an epidemiologist is assigned to each risk. The epidemiologist supports the gathering and analysis of relevant evidence, and ensures the quality of the analyses of astronaut surveillance data from the Lifetime Surveillance of Astronaut Health (LSAH) as part of the evidence base. These three individuals comprise the Risk Custodian Team that is responsible for providing a balanced view of the Human System Risk and developing Risk Posture recommendations based on the best available evidence. A detailed description of Risk Custodian Team responsibilities is laid out in the document, Don't Panic: A Risk Custodian's Handbook for the Human System Risk Board (SA-HDBK-001).

2.2 OFFICE OF THE CHIEF HEALTH AND MEDICAL OFFICER (OCHMO)

The OCHMO is responsible for policy and oversight of medicine at NASA for all of its workers on the ground, and in the air, sea, and space. OCHMO is the authority that manages Human System Risks for all human spaceflights at the Agency level in accordance with responsibilities and functions stipulated in The NASA Organization (NPR 1000.3) and NASA Health and Medical Requirements for Human Space Exploration (NPR 8900.1). The CHMO delegates this authority to the JSC CMO.

The OCHMO also owns the human health and performance standards which are housed within the NASA Space Flight Human System Standard (NASA-STD-3001). This is an Agency level, two-volume suite of documents which address the human needs for space flight. Volume 1 covers the NASA Standards needed to support astronaut health and Volume 2 covers system design that will maintain astronaut safety and promote performance. A standard (otherwise known as a technical standard) is a document that establishes uniform health, medical, engineering or technical criteria, methods, processes, and practices.

A Human System Risk or a set of Risks may engender one or more NASA Standards, which are tailored to particular programs with specific DRMs as program requirements. A requirement is a singular documented physical or functional need that a specific design, product or process aims to satisfy and that stems from a standard.

2.3 HEALTH AND MEDICAL TECHNICAL AUTHORITY (HMTA) AT JSC

The JSC CMO exercises HMTA decisional authority at their Center, including development of HMTA Risk, program and project positions that are determined to be risk-neutral or have a reduction in risk in support of all NASA human spaceflight efforts. The responsibility of the JSC HMTA is to manage Human System Risks through integration of standards into programmatic requirements. This is worked through programmatic and project insight and oversight, coupled with the appropriate support and involvement of subject matter experts. The JSC HMTA uses the HSRB to implement the management of the Human System Risks as described in this document. The JSC CMO delegates the management of the risk process and the HSRB to the Human Spaceflight Risk Reduction Manager and acts as the alternate Chairman of the HSRB.

2.4 HUMAN EXPLORATION AND OPERATIONS MISSION DIRECTORATE (HEOMD)

The HEOMD provides the Agency with leadership and management of NASA space operations and is responsible for execution of Human Exploration Programs related to human exploration in and beyond low Earth orbit. HEOMD provides funding to programs such as HRP, various human spaceflight programs, CHS and the Habitation - CHP SCLT. Spaceflight Requirements are owned by programs under HEOMD.

2.4.1 Crew Health and Safety (CHS)

The CHS is responsible for NASA's Astronaut Occupational Healthcare Program. CHS is supported by multiple entities that together ensure the physical and psychological health and well-being of astronauts. Medical and behavioral healthcare are provided for astronauts throughout their active careers. After leaving the astronaut corps, former astronauts receive continued monitoring to detect conditions related to spaceflight, and receive treatment when these conditions are identified. Data gathered throughout the astronauts' lifetime supports occupational surveillance and long-term health assessments. Information gained contributes to health maintenance and hazard mitigation for current and future astronauts. CHS also maintains the human health data systems that support crew health care and provide the evidence base to support risk modeling and epidemiological assessments of crew health. CHS seeks to align investments in occupational surveillance, clinical and epidemiologic data management, and long-term health tracking with high value risk mitigation targets agreed upon by the HSRB.

2.4.2 Human Research Program (HRP)

The HRP investigates and mitigates, to the extent that research and technology development is able, the highest risks to human health and performance for human space exploration; in turn HRP provides essential countermeasures and technologies for buying down risk. Strategically, the HRP conducts research and technology development that: 1) enables the development or modification of Agency-level human health and performance standards by the OCHMO and 2) provides the HEOMD with methods of meeting those standards in the design, development, and operation of mission systems. HRP aligns the Risk Postures in the Human Research Roadmap with that set at the HSRB. HRP seeks to align its research

portfolio with high value risk mitigation targets agreed upon by the HSRB.

2.4.3 Human Spaceflight Programs

Human spaceflight programs (and their control boards) such as the ISS Program, Multi- Purpose Crew Vehicle/Orion (MPCV), Gateway, Artemis, Human Landing System (HLS) and CCP own program requirements, design systems and ensure that operational resources are available to comply with standards established by the HMTA for the purpose of defining acceptable levels of Risks to the health and performance of the crewmembers. Human spaceflight programs also incorporate technologies resulting from the HMTA Transition-to-Operations (TtO) process geared towards risk reduction efforts through design and operations.

2.4.4 Habitation Systems Capability Leadership Team (Habitation - CHP SCLT)

The Habitation - CHP SCLT identifies capability gaps to advance Agency objectives, and develop strategies and roadmaps pertaining to Environmental Control and Life Support System (ECLSS) and CHP System technology development efforts and investments. It provides support for future human exploration architecture studies while exploring the overall strategy to evolve the ISS ECLSS and Crew Health Care System (CHeCS) into the Deep Space Exploration ECLSS and CHP Systems using ISS as a testbed.

2.5 HUMAN HEALTH AND PERFORMANCE DIRECTORATE (HHPD)

The HHPD charters the HSRB on behalf of the HMTA to produce and approve risk products in conjunction with HRP, CHS, and other human spaceflight projects, programs, and organizations. HHPD provides the personnel responsible for creating risk reduction products such as HMTA standard content, clinical practice guidelines or procedures for inflight, physiological countermeasures, technologies and system designs, and services such as training, rehabilitation, etc. The personnel provide these products as appropriate based on the funding levels provided by funding programs. The majority of personnel within HHPD are organized in three divisions, listed below.

2.5.1 Space Medicine Operations Division

Personnel in the Space Medicine Operations Division contribute medical, psychological, physiological and operational expertise, as well epidemiology support to the Human System Risk management process. There is nominally an operational risk custodian managing astronaut health for every human system risk. In addition, the Space Medicine Operations Control Board can be used for organization and prioritization of the integrated (medicine and scientific research) mitigation plan for each risk.

2.5.2 Human Systems Engineering and Integration Division

Personnel in the Human Systems Engineering and Integration Division contribute expertise in hardware development and certification, systems engineering, Human Systems Integration (HSI), human factors engineering, verification and validation of requirements, and space food.

2.5.3 Biomedical Research and Environmental Sciences Division

Personnel in the Biomedical Research and Environmental Sciences Division assess human adaptation to spaceflight and planetary environments, characterize risks to human space exploration, provide validated treatments and countermeasures, conduct peer reviewed applied research (in laboratories, analogues, and space) to provide evidence that addresses the Human System Risks. This Division also engages in operational support for all human spaceflight programs through the conduct and analysis of crew medical and environmental monitoring, astronaut training, sets standards for crew health and performance as well as spacecraft / habitat environments, confirm flight readiness, and assesses design and human performance for advanced space suit systems.

2.6 Other Directorates

Other directorates contribute to technology development, system designs, and evaluation of training and crew preparation for spaceflight. These include the Engineering directorate, Safety and Mission Assurance, Flight Operations Directorate, and the Science Mission Directorate.

3.0 RISK MANAGEMENT PROCESS

The overview of the risk management process applied to NASA's Human System Risk portfolio using CRM principles is shown in Figure 3. It consists of phases that capture the identification, analysis, planning, decision process, and tracking and implementation of risks, within a continuous process of documentation and communication.

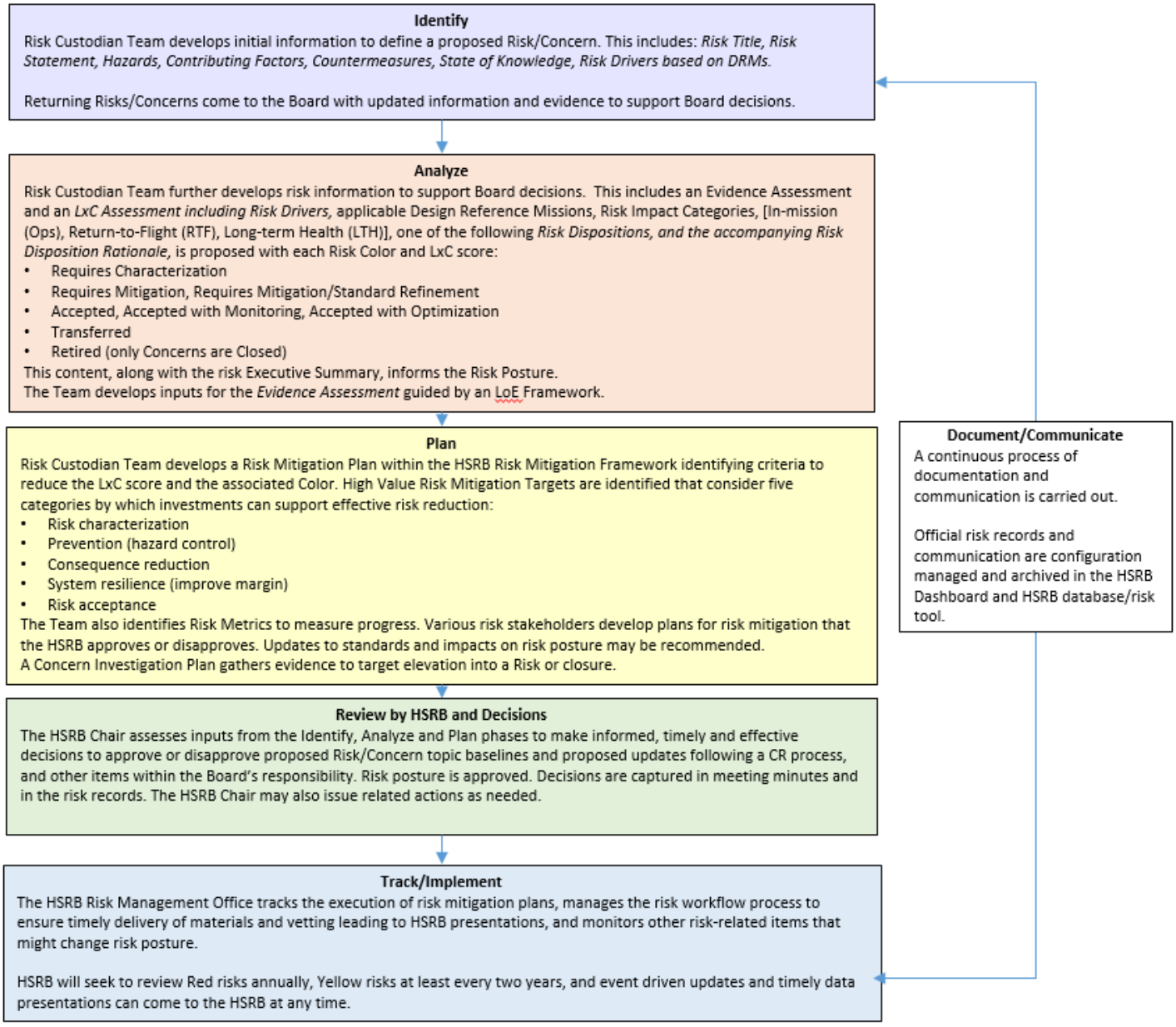

Figure 3: Human System Risk Management Process.

This figure describes the CRM process implemented by the HSRB as tailored to the unique nature and needs of Human System Risks.

3.1 IDENTIFY

The Identify phase has two purposes: (1) To identify if there is a new Risk or Concern that needs to be formulated and tracked; and (2) To identify if there is new/updated evidence that warrants an update of the Risk Posture for existing Risks and Concerns.

The initial information required includes a proposed a Risk Title and Risk Statement (with scenario clearly stated) and basic information such as associated Hazards, known Contributing Factors, existing Countermeasures, and State of Knowledge (as defined in Appendix D).

In managing Human System Risks, we consider two categories delineated by the level of maturity of their evidence base that supports their assessment:

- A Human System **RISK** is an undesired potential human health or performance outcome for the crew that has a clear consequence and attendant likelihood supported by evidence for a given DRM. It is captured in a Risk Statement (see Appendix D) that is a concise description of the driving scenario and the undesired negative outcome. This statement is written in such a way as to inform the development of a mitigation plan to be acted upon and tracked.
- A Human System **CONCERN** is an undesired potential human health or performance outcome for the crew for which there is not sufficient evidence to allow a Likelihood versus Consequence (LxC) assessment for any DRM. When sufficient evidence is gathered or vetted to support the item of concern, it may be elevated (as approved by the Board) to a Risk that will then have additional associated risk information. The purpose of the Concern category is to identify domains where characterization is needed to determine whether an issue is of sufficient magnitude to be considered for mitigation.

The list of Risks and Concerns managed by the HSRB as of this writing is shown in Appendix C. New Risks and Concerns may be identified by anyone and can be brought forward to the Board in coordination with the HSRB Risk Management Office. The Board expects proposers to provide evidence that the Risk or Concern meets the above criteria and encourages discussion of these candidate items with appropriate stakeholders and subject matter experts.

Occasionally, risk products may be identified that are of relevance to an existing program (such as CCP or Orion). When identified, these are elevated for awareness through the HMTA Representatives to those programs and their program boards. The HSRB manages Risks that are vehicle-independent and that impact the crew across multiple DRMs. The HSRB will provide relevant services to communicate and evaluate Human System Risks that are relevant to established and evolving programs, but the HHPCB is responsible for timely updates and responses to program-specific Risks.

Risk Custodian Team

The HSRB, in coordination with the respective divisions for research and operational experts and epidemiologists, designates the appropriate custodians for the Risk or Concern. The Risk Custodians identified are responsible for integrating the relevant information and evidence critical for establishing and updating the Risk Posture. The relevant information and evidence is collected from multiple

stakeholder organizations and is further defined in Section 3.2. The team works together to coordinate content development among relevant risk stakeholders. It is an expectation that the Risk Custodian Team shall meet with the OCHMO Standards team and the biostatisticians at least once during the Risk update process. The Standards team will work with the Risk Custodian Team to review the current applicable OCHMO Standards and determine if new standards are needed or existing standards should be updated. The biostatisticians should be consulted to review any quantitative claims about data.

For a ***new* Risk or Concern**, a Risk Custodian Team is assigned that provides the Risk Manager the following basic information:

1. Risk/Concern Title
2. Risk/Concern Statement
3. Risk/Concern Summary slide including (among other fields):
    a. State of Knowledge
    b. Hazards associated with the Risk/Concern
    c. Contributing Factors (which may include other Human System Risks)
    d. Countermeasures that exist, are demonstrably feasible, or are beyond Technology Readiness Level 7 required to mitigate Risk Posture
    e. Likelihood and Consequence scores delineated by DRM and applicable risk impact categories with supporting risk drivers, proposed dispositions and associated rationale (applicable to Risks only).

If the current information is deemed too premature by the Risk Manager, the topic will be included by the HSRB Risk Management Office in a list of topics that can be watched and revisited at a later time when the supporting information and circumstances indicate a need for elevation.

If the Risk Manager decides that there is sufficient evidence to support a new Risk or Concern, then the proposer develops a complete proposal that provides a review of the evidence that supports the Risk or Concern. This information is put into an official template that includes an Executive Summary write-up as a narrative form of the evidence supporting the Risk Posture.

For a ***returning* Concern**, the Risk Custodian Team identifies any significant new information that supports the Board's review of its possible elevation to a Risk. If there is no new evidence to review, the team must present a Concern package according to the official template that requests a decision from the Board regarding whether the Concern should continue to be tracked or closed.

For a ***returning* Risk**, the Risk Custodian Team brings forward a review of new evidence since the last update and recommends updates to Risk Dispositions as warranted. The team begins the update process with a meeting with the Risk Manager and coordinates with the HSRB Risk Management Office on the development of the information package in the official Change Request (CR) kickoff template that will be presented to the Board.

The following sections provide more information on the required information and analysis.

3.2 ANALYZE

Once the Risk Custodian Team collects the evidence supporting the Risk, they enter the Analyze phase that includes evaluating the collected evidence to develop the narrative that explains the

recommendation for a new or updated Risk Posture. The following steps are relevant in establishing Risk Posture:

1. Identification of risk drivers
2. Understanding risk DRM applicability
3. Delineation of risk impact categories
4. Assessment of Likelihood and Consequence scores
5. Assignment Risk Dispositions per DRM with their respective Risk Disposition Rationales
6. Communication of Level of Evidence (LOE)
7. Summarization of Risk Posture information

3.2.1 Risk Drivers

Risk Drivers describe how the spaceflight hazards (Section 1.0), which are a feature of the spaceflight environment, modify Risk Posture depending on changing mission attributes. Risk Drivers are not risk specific but change depending on the mission objectives and can drive increased mission risk across multiple Human System Risks. In this way they are different from Contributing Factors which are called out specifically from a single risk perspective. Identifying the potential drivers of Human System Risks allows 1) a clearer understanding of the origin of the risk and potential areas for risk mitigation, 2) an improved understanding of the potential relationships between Risks, and 3) an improved ability to prioritize risks for stakeholders. The following is a list of drivers pertinent to Human System Risks and includes spaceflight hazards, contributing factors, and other modifiers such as time of exposure or resource constraints.

Time (mission duration) and environmental exposures

As mission duration increases, exposure to environmental hazards increases. This has the effect of degrading human crew from time of launch until return to Earth. Mission duration is a Risk driver in the following ways:

Gravity Environment

Exposure to a gravity environment that is less than Earth-normal begins a process of adaptation; some of these adaptations create issues for human bodies that developed to function in a 1G environment.

Radiation Environment

Risk from exposure to changing radiation environments is both duration-dependent and intensity dependent and may have in-mission or long term health impacts that are time-exposure dependent.

Isolation and Confinement

Increasing time in the isolation expected in space missions increases the risk of psychological,

physical, and mental health issues for crew.

Hostile Closed Environment

While in a vehicle or space suit, perturbations in local environmental conditions including air quality, temperature, accelerations, movement restriction, and more can result in illness, injury, or inability to perform critical tasks. Examples include launch and landing loads, suit and vehicle carbon dioxide ($CO_{2)}$ levels, and amount of time crew spend in a hot or cold environment due to insufficient Environmental Control and Life Support System (ELCSS) capability.

Distance from Earth

Real-time Communications vs. store and forward communications

As distance from Earth increases, communication lags are expected to not only delay ground support in to crews, but also to force an operational shift from real-time support to greater crew responsibility, implementation of intelligent support software, and store-and-forward communications as part of enabling greater crew autonomy. The success of implementing this shift will depend on having both effective integrated data systems and being able to change operational approaches. Overall reliability of the communications chain back to Earth depends on the availability and reliability of each node in the chain. Some mission DRMs are expected to have periods of no communication with ground support.

Time to definitive care (evacuation)

As distance from Earth increases, the timeframe required to get to definitive medical care increases. For each DRM, medical evacuation timeframes must be considered as a drivers of health risk for crews. In particular, for Mars DRMs, medical evacuation will not be possible and this shifts the Risk Posture for crews.

Consumables Resupply

As distance from Earth increases operational system trades are likely to target mass and volume needed for food, pharmaceuticals, and medical equipment/consumables for savings. In missions where resupply is possible, the risk of interruption of the supply chain becomes higher with greater distance from Earth. In Mars DRMs, it is not possible to resupply and pre-supply options have severe disadvantages due to shelf life.

Vehicle resource constraints (mass, power, volume, data)

The limitations on mass, power, and volume will be determined by the mission goals and attributes. Different mission envelopes will carry different Risk Posture based on the total available mass, power, volume, and data that can be traded among vehicle systems.

Vehicle habitable volume and capability

Hazards such as isolation and confinement and closed/toxic environments drive risks to crews that are heavily dependent on net habitable volume which is different from total resource volume. Limited habitable volume may result in the restriction or exclusion of behavioral health impactors

such as private crew quarters and amenities that can help offset behavioral and interpersonal issues. Programs should expect decrements in human performance both of individuals and of teams as capabilities and countermeasures are sacrificed.

Crew selection and assignment

Crew medical and behavioral profiles must be understood, formalized into standards, and accommodated in mission planning. Mixed government and private crews may result in more medical and behavioral risk than was originally considered during mission planning. This is because it is unclear if commercial and private astronauts will undergo the same selection procedures (both medical and psychological screening) as NASA astronauts, and it is unclear if teaming evaluations will be done for private and commercial crew astronauts, NASA astronauts and other government-sponsored astronauts.

High risk activities

Certain missions will require human crew activities that pose greater risk to both crew and mission. Some examples of high risk activities are listed below:

- Lunar or planetary landing and exploration may increase the likelihood of musculoskeletal traumatic injuries and dust exposure issues.
- Increasing numbers of extravehicular activities (EVAs) will increase the likelihood of decompression sickness and suit- or activity--related injuries.
- Increasing time outside Earth's magnetic sphere will increase the radiation exposure of crews beyond that which has been experienced in low earth orbit.
- If crews cannot shelter effectively during a solar particle event, distance from a radiation shelter during an EVA may affect the likelihood of acute radiation sickness if crews cannot shelter effectively.

Organizational risk tolerance

In some DRMs, the Agency may be forced to choose prioritization between mission and mission objectives or loss of crew life or permanent disability. This is in part due to the inability in a Mars DRM to return a sick or injured crewmember to the Earth for care. This responsibility is held at the level of the CHMO, but where Agency risk tolerance is known, it should be considered in assessing Risk Posture.

3.2.2 Design Reference Missions (DRMs)

The HSRB uses a set of four DRM categories against which to assess Risks: Low Earth Orbit (LEO), Lunar Orbital, Lunar Orbital + Surface, and Mars. These categories are derived from a subset of the risk drivers discussed above starting with separation into short and long term time frames to represent the effect of duration on the Human System Risk. Table 1 shows corresponding parameters for each DRM representing associated hazards and general mission attributes to guide LxC interpretation. For the purposes of communication to OCHMO and stakeholders, these definitions seek to be as concise as

possible, with only essential detail included.

Table 1: Official HSRB Design Reference Mission (DRM) Categories

DRM Categories	Mission Type and Duration	Gravity Environment	Radiation Environment	Vehicle/Habitat Design	Distance from Earth		EVA
					Evacuation	Communication	Frequency
Low Earth Orbit	Short (<30 days)	Microgravity	LEO-Van Allen (<5-15 mGy)	Mid-sized volume, resupply	1 day or less	Real time	1-4 EVAs
	Long (30 days-1 year)	Microgravity	LEO-Van Allen (5-150 mGy)	Mid-large optimized volume, resupply	1 day or less	Real time	1-10 EVAs
Lunar Orbital	Short (<30 days)	Microgravity	Deep Space-Van Allen (15-20 mGy)	Small volume, self contained, resupply	3 – 11 days	Real time	Contingency EVA only or very few EVA
	Long (30 days-1 year)	Microgravity	Deep Space (175-220 mGy)	Mid-sized volume, self contained, limited resupply	3 – 11 days	Real time	Contingency EVA only or very few EVA
Lunar Orbital + Surface	Short (<30 days)	Microgravity & 1/6g	Deep Space-Van Allen (15-20 mGy)	Small volume, resupply	3 – 11 days	Real time	5 EVAs, some back to back
	Long (30 days-1 year)	Microgravity & 1/6g	Deep Space (100-120 mGy)	Mid-large sized optimized volume, limited resupply	3 – 11 days	Real time	3-4 EVA per week, 20-24 EVA hrs. per week
Mars	Preparatory (<1year)	Microgravity	Deep Space (175-220 mGy)	Midsized optimal volume, limited resupply, closed loop environment	Days – weeks	Controlled - Delayed	Contingency EVA only or very few EVA
	Mars Planetary* (730-1224 days)	Microgravity & 3/8g	Deep Space – Planetary (300-450 mGy)	Midsized optimal volume, no resupply, closed loop environment	Mission duration	No real time	2 crew x 8-hour EVA x 20 EVA days

*Based on memo - HEO-DM-1002 HEO Systems Engineering and Integration (SE&I) Decision Memo on Mars Mission Duration Guidance for Human Risk Assessment and Research Planning Purposes

Low Earth Orbit DRMs have two categories:

- Short (<30 days) is intended to approximate LEO missions that include crew going to either the ISS, another orbital outpost, or staying in a smaller vehicle that approximates a capsule or space shuttle type experience.
- Long (>30 days to 1 year) is intended to approximate LEO missions to either the ISS or a comparable vehicle.

Lunar Orbital DRMs have two categories:

- Short (<30 days) is intended to approximate a short duration stay in orbit for crews either at a Gateway type facility or a smaller vehicle.
- Long (>30 days to 1 year) is intended to approximate a long duration stay in a lunar orbital outpost such as Gateway.

Lunar Orbital + Surface has two categories:

- Short (<30 days) is intended to approximate an Artemis 1 type mission there entire mission is less than 30 days where part or all of the crew spend some portion of the mission involves partial gravity of the

lunar surface, a lunar surface habitation or vehicle stay, and EVAs on the lunar surface.

- Long (>30 days to 1 year) is intended to approximate extended lunar stays in an Artemis-type program where part or all of the crew spend some portion of the mission involves partial gravity of the lunar surface, a lunar surface habitation or vehicle stay, and EVAs on the lunar surface.

Mars has two categories:

- Mars Preparatory (< 1 year) is intended to approximate a mission that is likely performed in Lunar Orbit to simulate Mars transit, but invokes artificial communication delays and tests/validates new systems and technologies. Because of the partial or complete reliance on new systems and operational approaches, there is expected to be elevated risk over a Lunar Orbital Long type mission. Some mitigation of that risk can be expected through control of communication delays and a continued option for evacuation if needed.
- Mars Planetary (730 to 1224 days) is intended to approximate a Mars mission including time on the planetary surface in partial gravity conditions for some or all of the crew. Guidance from HEO-DM-1002 is used to approximate the mission parameters most likely to be seen in this type of mission.

These broad- categories are scoped to allow the flexibility to provide risk characterizations and assessments that will be applicable to a range of human space exploration missions including those yet to be defined. While the DRMs are not directly mapped to programs, the intent is to allow relevant programs to interpret what Risk Posture is relevant to informing their needs based on known mission attributes. The board communicates in terms of missions rather than programs because multiple vehicle programs may contribute to a single overall mission. There can be a tendency for programs to focus on their portion of the mission only and underestimate their contribution to total mission risk. The Human System Risks can be spread across multiple programs in a single mission and it is the board responsibility to look at and communicate the big picture of risk. This is designed to facilitate discussion between the HMTA delegates and those programs. Updates to the DRMs and their parameters may be initiated by the HSRB Chair as necessary to ensure that Risk Posture recommendations are reasonably representative of Agency needs, and in response to the development of mission information as determined at the Agency-level.

3.2.3 Risk Impact Categories

There are three potential categories where risk consequence can impact either the crew or the Agency. These are used in the LxC matrix below (Figure 4) to illustrate the driving Risk Posture in each DRM category as appropriate.

1. **In-Mission Risk (Ops)** –the Risk Posture for crews in-mission defined by successful launch until successful and safe egress from the landing vehicle. The *Crew Health* impact subcategory identifies health issues while the *Mission Objectives* impact subcategory identifies crew performance decrements that can result in loss of mission objectives if realized.
2. **Flight Recertification** – applies when specific risk manifestation impacts the crewmember's physical or mental health after a mission, thereby delaying their flight certification and flight recertification status. This applies throughout the career of an astronaut.
3. **Long Term Health (LTH)** – the lifetime impact of spaceflight on physical and mental health and

performance of astronauts post flight including post-career. The LTH category consists of the *Health Outcomes* impact subcategory which includes medical conditions resulting from career exposures to the spaceflight environment, and the *Quality of Life* impact subcategory which identifies decrements in the ability of a post-flight astronaut to perform daily living activities as a result of career exposure to the spaceflight environment.

3.2.4 LxC Assessment and Colors

For a particular DRM, a risk scenario is a sequence of credible events that specifies the evolution of a system or process from an assumed current state to an undesirable state, and is captured in the Risk Statement. In turn, each risk scenario can have up to 5 potential categories of consequence with associated likelihood categories. Information on each consequence/likelihood combination associated with the risk is summarized according to where it lies in the 5x5 "LxC matrix" as shown in Figure 4. The Consequence categories are defined for each Risk Impact Category and Sub-category in the chart at the bottom of Figure 4 and are meant to apply to all Risks. Depending on the Risk Impact Category, the Likelihood categories are also defined on a 1-5 scale corresponding to specified ranges of event probabilities (upper-left section of Figure 4), taking the level of uncertainty associated with the risk evidence base into account with any risk scenario defined for a particular DRM. The risk scenario is a sequence of credible events that specifies the evolution of a system or process from a current state to an undesirable state, and is captured in the Risk Statement. Figure 4 shows the 5x5 risk matrix used for Human System Risk assessment with definitions for likelihood and consequence across their defined scales and across risk impact categories. The numbers in the cells of the LxC matrix are priority weights adopted from the ISS scorecard, which for each Risk, maps relevant combinations of likelihood and consequence categories for a given DRM and Risk Impact Category to "LxC Scores" that can be adopted by the HSRB for between-risk prioritization. Note that while the appearance is similar to program risk matrices, each risk matrix has its own definitions and these do not necessarily result in similar assessments across different matrices. In determining the particular set of priority weights displayed in Figure 4, the consequence category is given slightly more weight than the likelihood category. At a higher level, the maximum LxC Score for each Risk is mapped into one of three Risk Colors (green, yellow, or red) to readily communicate the most essential information in each risk scenario to management and program officials. At present the rule for assigning Risk Colors is: red (maximum LxC Score $\geq$ 20), yellow (11 $\leq$ maximum LxC Score $\leq$ 19), and green (maximum LxC Score $\leq$ 10). A shorthand terminology used in the rest of this document is that a "Risk is (red, yellow, or green)" means the Risk Color of its maximum Score is (red, yellow, and green). As an example, for a given DRM, Risks that are red admit at least one risk scenario with a very serious consequence/likelihood combination (maximum LxC Score $\geq$ 20). In general, these Risks should be prioritized for mitigation over yellow Risks, whose worst consequence/likelihood combination results in a Score between 11 and 19, which in turn would be prioritized over green Risks.

The LxC matrix, while informed by the best available evidence, (the numbers in the cells are priority scores defined in Section 3.8.3) is not designed to be a statistically precise tool for evaluating risk, but nevertheless serves to provide concise and effective messaging to stakeholders on Risk Posture.

LIKELIHOOD RATING			
	In-Mission	**Flight Recertification**	**Long Term Health**
5 Very High	More likely to happen than not during the mission or probability (P) >10%	Very likely to happen. Controls are insufficient or P> 10%	Likelihood is very high OR >10% excess risk
4 High	Likelihood is high during the mission or 1%<P≤10%	Likely to happen. Controls have significant limitations or uncertainties or 1%<P≤ 10%	Likelihood is high OR 6-10% excess risk
3 Moderate	May happen during the mission or 0.1%<P≤1%	Not likely to happen. Controls exist with some limitations or uncertainties or 0.1%<P≤1%	Likelihood is moderate OR 3-6% excess risk
2 Low	Unlikely to happen during the mission or .01%<P≤0.1%	Not expected to happen. Controls have minor limitations or uncertainties or 0.01%<P≤0.1%	Likelihood is low OR 1-6% excess risk
1 Very Low	Nearly certain to not occur in-mission or P≤0.01%	Extremely remote possibility that it will happen. Strong controls in place or P≤0.01%	Likelihood is very low OR < 1% excess risk

L x C Matrix

LIKELIHOOD						
5	10	16	20	23	25
4	7	13	18	22	24
3	4	9	15	19	21
2	2	6	11	14	17
1	1	3	5	8	12
	1	2	3	4	5
	CONSEQUENCE				

Time frame Expected Need for Mitigation	
Near	0 < 2 Years
Mid	2-7 Years
Far	> 7 Years

Risk Score Card values are constant across all risks and prioritize consequence over likelihood.

CONSEQUENCES		1	2	3	4	5
IN MISSION	**Crew Health Impact** OR **Mission Objectives Impact**	Temporary discomfort / Insignificant impact to crew performance and operations – no additional resources required	Minor injury/illness that can be dealt with by crew without ground support, minor crew discomfort / Minor impact to crew performance and operations – requires additional resources (time, consumables)	Significant injury/illness or incapacitation that requires diagnosis and/or treatment support from ground, may affect personal safety / Significant reduction in crew performance, threatens loss of a mission objective	Critical injury/illness of one crew member requiring extended medical intervention and support, may result in temporary disability / Severe reduction of crew performance that results in loss of multiple mission objectives	Death or permanently disabling injury/illness affecting one or more crewmember (LOCL/LOC) / Loss of mission due to crew performance reductions or loss of crew
FLIGHT RECERT	**Crew Flight Recertification Status**	Immediate flight recertification status	Flight recertification status within 3 months with limited intervention	Flight recertification status within 1 year with nominal intervention or restricted flight status	Flight recertification status requires extended medical intervention and takes > 1 year	Unable to be Recertified for Flight Status, premature career end
LONG TERM HEALTH	**Health Outcomes** OR **Quality of Life**	Career related short term self-resolving medical conditions / No impact on quality of life OR independence in activities of daily living	Career related medical conditions manageable with outpatient medical treatments / Minor, short-term impact on quality of life OR rare support required for activities of daily living	Treatable career related medical condition that requires hospitalization for management / Moderate long-term impact on quality of life OR may require some time-limited support for activities of daily living	Chronic career related medical condition requiring intermittent hospitalization or nursing care / Major long-term impact on quality of life OR requires intermittent support for activities of daily living	Career related premature death or permanent disability requiring institutionalization / Chronic debilitating impact on quality of life OR requires continuous support for activities of daily living

Assumptions for Long Term Health Risk Matrix:
- *Long Term Health extends from the end of the post mission time period and covers an astronaut's lifetime.*
- *Conditions considered within the LTH Risk Matrix are those that 1) are related to the astronaut career, 2) are beyond those expected as part of natural aging, and 3) include acute, chronic and latent conditions.*
- *Quality of Life is defined as impact on day-to-day physical and mental functional capability and/or lifetime loss of years*

Figure 4: Likelihood & Consequence (LxC) Scale Definitions and LxC Matrix used for scoring Risks

The likelihood and consequence are defined as follows:

Likelihood (L) - The quantitative or qualitative probability that the adverse events and associated consequences defining a Risk Scenario will occur.

For each Risk Impact Category, the HSRB assessments of likelihood category (1- 5) are shown for ranges of likelihood indicated in Figure 4 (upper left) and established to guide the selection of the most applicable consequence categories. While the consequence categories remain the same across all risks and DRM's, the assessed likelihood categories will differ for each combination of Risk and DRM. For purposes of assigning likelihood categories, actual likelihoods (i.e. probabilities of adverse events) are assessed at a measure of central tendency for the most likely human health or performance adverse outcome. However for proper documentation, an uncertainty metric or confidence interval for these probabilities should be provided. In the case of Human System Risks it is understood that while initially developing an evidence base, some likelihoods will not be quantifiable. Part of the purpose of research in these domains is to help inform those quantitative estimates. Examples of acceptable quantitative estimates include Probabilistic Risk Assessment (PRA) calculations used by the NASA Safety and Mission Assurance directorate, and the Integrated Medical Model (IMM) which was transitioned to operations in 2017. Additionally, historical data on incidences and relevant terrestrial analog data are considered.

Consequence (C) – – A possible crew health and/or performance decrement associated with a given risk. For each Risk Impact Category and subcategory, negative consequences of risk scenarios are classified into five categories of severity in terms of decrements to crew health and performance. In the lower half of Figure 4, the HSRB definitions of consequence category are also shown for each risk impact category and their respective crew health and performance. These are intended to enable selection of an appropriate consequence across the spectrum of impacts possible in the domain of human health and performance. The consequence with the highest likelihood drives the consequence score for that Risk Impact Category within the DRM being assessed. Only one Sub-Impact Category shall be used to inform the LxC score for each Impact category. These consequence definitions are all qualitative, definitions but are expected where possible to be informed by quantitative calculations based on expected changes in Risk Drivers.

Uncertainty – Quantitative assessment will be used to communicate the uncertainty of any reported point estimates or distributions describing a likelihood and/or consequence of risks. Uncertainty metrics could include confidence limits, standard errors, posterior probabilities, and credible intervals. In the case of qualitative estimates of risk, the subject matter experts will provide an assessment of uncertainty choosing from high, moderate, or low based upon their expert evaluation.

The purpose of uncertainty estimates is to give appropriate insight to mission planners, managers, and crew of the precision of our knowledge in these domains and to enable informed consent where applicable.

It is essential that the likelihood and consequence match the available evidence to ensure appropriate risk dispositions for each DRM. For a given Risk, an LxC score is assigned to each feasible consequence/likelihood combination by risk impact category and by DRM as needed. In turn, for each DRM and impact category, the Risk Color is assigned based on the maximum LxC Score according to the

procedure described in Sec 3.2.4. In some cases when the LxC matrix is not applicable or likelihoods or consequences are not able to be defined, the color gray is used. Risk Colors serve as communication tools for the development of the HSRB's Risk Posture updates to stakeholders.

The LxC scores and colors are documented in the risk package presented to the HSRB and are captured in the Risk Summary record. The best assessments of likelihood, likelihood category, consequence, and consequence category supported by current evidence are proposed by the Risk Custodian Team according to the definitions in Figure 4. These assessments should consider the likely effects of any relevant currently operational countermeasures when determining current Risk Posture. A countermeasure refers to any standard, design specification, operational procedure or rule, or technology that has been deemed by the HSRB to be likely to mitigate risks to crews in one of the three impact categories. For the purposes of assigning consequence or likelihood categories for obtaining LxC scores, proven countermeasures, countermeasures that have shown high potential value in the research arena, that are not yet used or operational can be considered and noted as a countermeasure in the Risk Summary record.

For example, the Muscle Risk Posture for a one-year Gateway mission (Lunar orbital + surface DRM) is assessed against the assumption that an exercise device that provides astronauts with the ability to achieve the same level of fitness as the current capabilities in use on the ISS will be in place.

HMTA Crew Health and Performance Officers are expected to communicate to programs that the Risk Posture is dependent on the successful implementation of listed countermeasures in operations or vehicle design. Assessment of program inclusion of required countermeasures is undertaken at the HHPCB in the course of normal business. If programs fail to implement the countermeasures that support a given Risk Posture, the HHPCB has the responsibility to determine programmatic risk impact in the larger risk context for that program.

The timeframe within which mitigations are expected to be reasonably completed (near, mid and long-term) is identified and noted at a high level. This is to provide insight to Crew Health and Performance Officers and programs as to the expected lead time for major risk mitigations and when they may impact those programs.

3.2.5 Risk Color

The overall severity of Risks is measured by risk colors at the highest levels. These colors are determined by where the LxC scores are plotted on the 5x5 risk matrix (Figure 4). The numbers in the cells are priority scores used to facilitate the interpretation of LxC scores within a risk prioritization scheme to be adopted by the HSRB. The LxC scores are based on the best interpretation of evidence using qualitative or quantitative means according to L and C scale definitions. Embedded in the LxC score determination is an assessment of the level of uncertainty associated with the risk evidence base. For a given DRM, Risks that are red have relatively higher LxC scores than Risks that are yellow and green. As such, red Risks are generally prioritized over yellow Risks which are prioritized over green Risks. When comparing risks within the same color region, the HSRB weights the consequence score more than the likelihood score.

3.2.6 Risk Dispositions

Accompanying each set of DRM-specific LxC scores and associated LxC colors, is the Risk Custodian Team's assessment of the Risk Disposition which represents the HSRB's overall position on the state of the risk assuming known countermeasures and monitoring will be implemented in a given DRM. The options for HSRB Risk Dispositions are detailed below. Once assigned, the Risk Disposition rationale statements are documented in the risk package.

3.2.6.1 Disposition: Requires Characterization

A Risk ***Requires Characterization*** when the underlying nature of the Risk (e.g. mechanism of its occurrence) is not understood sufficiently to determine whether further investment in mitigation is worthwhile or if there are large gaps in knowledge that preclude effective mitigation at other levels such as prevention or consequence reduction. This indicates that additional evidence needs to be developed or collected to inform consideration of mitigation and countermeasure development or risk acceptance. That evidence may be supplied by research studies, occupational surveillance, clinical outcomes, or other means.

3.2.6.2 Disposition: Requires Mitigation, Requires Mitigation/Standard Refinement

A Risk that ***Requires Mitigation*** indicates that the current countermeasures are believed to be inadequate and the risk to the crew for a given DRM warrants work to develop additional or improved countermeasures, technologies, or standards to improve Risk Posture. In cases where both characterization and mitigation are recommended by the Risk Custodian Team, the disposition ***Requires Mitigation*** will be used only when there is sufficient characterization already accomplished to reasonably determine that the risk is worth further investments in mitigation. When the mitigation plan requires the update of related standards, the disposition is specified as ***Requires Mitigation/Standard Refinement***. The rationale and the description for standards updates are provided in the Risk-Standards-Requirement section of the risk package.

3.2.6.3 Disposition: Accepted, Accepted with Monitoring, Accepted with Optimization

A Risk is ***Accepted*** by the Board when countermeasures are deemed effective and efficient, or no further risk reduction is considered appropriate at that time. The Board may determine that countermeasures are adequate and available (e.g. technology is already flying or transitioned to operations), and will be included in future programs (e.g. if a standard is written) such that risk to crew is minimal within the DRM parameters. The Board assigns acceptance of risk to future programs contingent upon the implementation of the assumed countermeasures, standards, etc. by future programs.

A Risk can be accepted regardless of Risk Color (i.e. red, yellow, or green). Even if a Risk Color is yellow or red, Risks may be accepted for the following reasons: (1) If required resources to mitigate the risk are not achievable, acceptance can facilitate risk-informed decisions to balance Agency and crew interests; (2) if the cost of further mitigation is not worth the marginal improvement in Risk Posture or is unlikely to improve Risk Posture in a meaningful timeframe; or (3) if continued mitigation of the Risk in question

could result in an elevated mission risk in other areas, such that under the existing trade space, NASA would be unable to minimize the overall Human System Risk.

There are two instances where risk acceptance requires forward work that is noted in the disposition: (1) ***Accepted with Monitoring***: when the risk acceptance of a particular risk depends on having sufficient insight into the state of the human system to inform operational action in-mission, monitoring may be necessary to ensure prompt intervention by crews or mission control; and (2) ***Accepted with Optimization*****:** when it is determined that additional countermeasure optimization is needed to minimize the utilization of resources of a particular DRM or that it will likely buy margin for human system resilience. Additional investment in managing a single risk may buy additional system resilience when considering Risk-Risk interactions and dependencies and provide value to overall system risk reduction, while the individual Risk is still accepted.

HSRB will review accepted Risks to assess any new evidence that may impact the criteria for acceptance. As needed, the HSRB Chair will recommend elevation of accepted Risk discussions to the OCHMO Level 1 Board. For example, where the standard or acceptable limit is not met for in-mission health and performance, crew flight recertification status, or long term health, the acceptance of that Risk in that particular DRM will be based on an HSRB recommendation to the OCHMO Level 1 Board.

In cases where a given program is unable to include countermeasures and monitoring captured in a Risk Disposition or when a program is initiated and there may be rejection of requirements, then the Risk Custodian Team returns to the Board with a reassessment of the LxC and any associated change in the risk disposition. The HMTA delegates may also request this risk re-assessment to assist with communication regarding potential programmatic risks that should be considered. These programmatic risks are primarily managed by the HHPD Control Board.

The dispositions below are not DRM specific.

3.2.6.4 Disposition: *Transferred*

At times, it may be advantageous to reorganize risk structure. This can occur when specific risks are recognized to be contributing factors to another existing risk; specific risks are believed to be sufficiently characterized and mitigated such that they can now be considered as part of larger, aggregating risks; or a different risk structure is likely to improve communication regarding impact to crew health or performance outcomes. In these cases, a Risk may be ***Transferred*** to the domain of a different Risk. For a Risk to be transferred, the rationale for transfer must be clearly stated and the HSRB Chair must approve. Given that the transfer of any individual Risk to another Risk is a unique event, the HSRB Chair, in collaboration with the transferring and accepting Risk Custodian Teams, shall define the records, evidence, and process needed for the transfer of a particular Risk. Once a Risk is transferred, the accepting Risk Custodian Team has full responsibility for the new Risk. For archival purposes, transferred Risks will be labeled as 'Transferred to _____ Risk" such that the historical evolution of the management of the Risks is made transparent.

3.2.6.5 Disposition: *Retired*

There are limited instances when a Risk is considered ***Retired***. Based on the evidence, a retired Risk is ***Retired*** when it has a consequence of sufficiently low magnitude that its assessment is not warranted on a regular basis; however, its existence as a noted Risk will be maintained in the risk database. A Retired Risk may be reviewed for major changes in DRMs developed by the Agency or at the request of the HHPCB.

3.2.6.6 Disposition: *Closed*

This category only applies to Concerns. Any Concern considered by the Board that is not found to have sufficient supporting evidence to be elevated to a Risk will be ***Closed***. If the Board determines that a closed Concern should be elevated to a Risk, it will enter the process for a new Risk as described in Section 3.1.

3.2.7 Evidence Assessment

For each Risk, the Risk Custodian Team gathers various types of data that comprise the best available set of evidence representing operational, medical, environmental and occupational surveillance, and scientific research and human performance to interpret and support the case for the Risk Posture (Figure 5). Within NASA, the HRP Evidence Reports and the occupational surveillance data maintained by the LSAH may serve as primary human health and performance risk-evidence sources and relevant terrestrial literature is also be considered as part of setting a Risk Posture. The Risk Custodian Team assesses the available evidence and brings forward a recommendation for their assigned Level of Evidence at scheduled Risk updates.

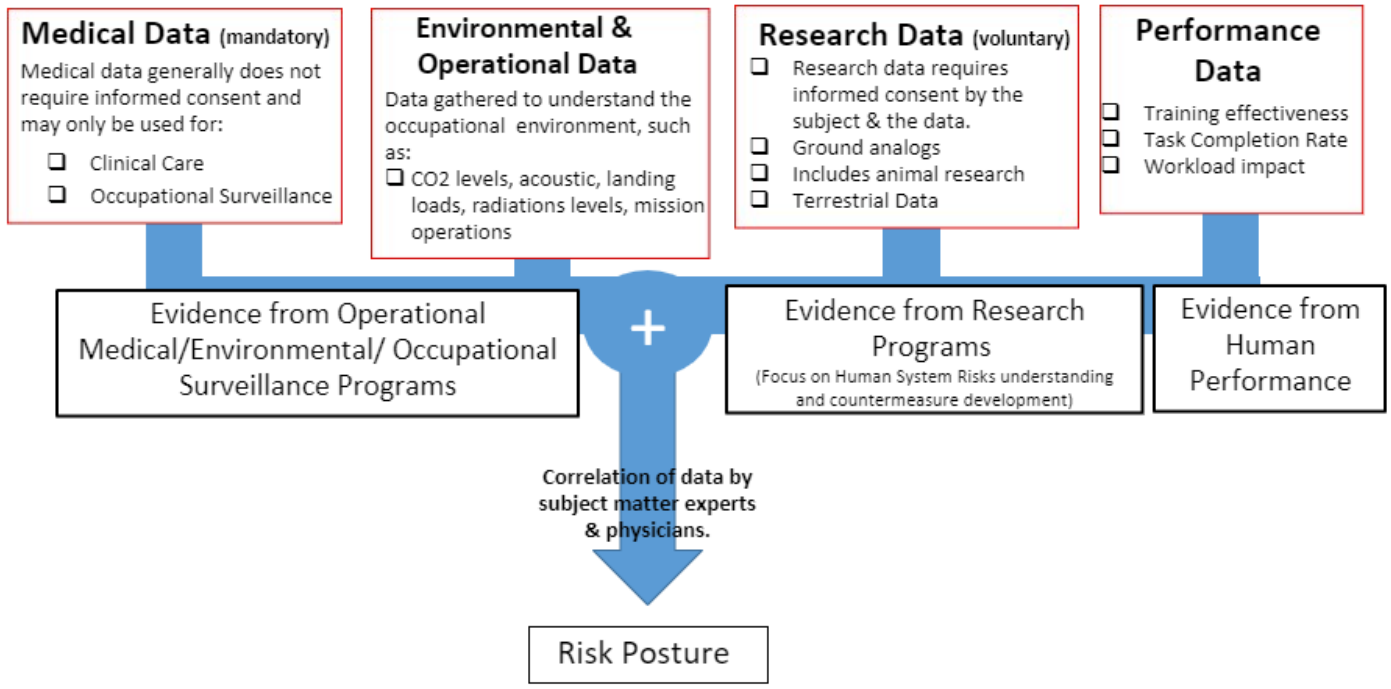

Figure 5: Sources of Evidence Considered in Assessing Risk Posture and Risk Summary

The goal of providing a Levels of Evidence assessment to the risk Board is twofold: (1) to communicate, the Risk Custodian Teams' best assessment of the strength of the evidence that supports the recommendations for the Risk Posture for each DRM; and (2) to communicate the strength of evidence behind specific assertions which are represented by individual lines (causal relationships) on the Directed Acyclic Graphs (DAGs). The lines on the DAGs indicate key areas of understanding needed to characterize or mitigate the risk. Evidence assessment for DAGs is addressed in Appendix G. This section focuses on the first goal. The Levels of Evidence assessment is a best estimate at a given moment in time: evidence pertinent to Human System Risk Posture and mitigation comes from a wide variety of sources, changes frequently over time, and requires significant expertise to interpret correctly. As a result, the Levels of Evidence assessments are expected to evolve.

The purpose of presenting the assessed Levels of Evidence at the HSRB is to offer an opportunity for feedback from the HH&P community and engage with broader expertise. If the Board does not offer change recommendations or revisions then the Risk Custodian Team's best assessment of the Level of Evidence becomes part of the configuration managed risk record until the next Risk update.

Format for the Levels of Evidence Assessment

Risk Custodian Teams use a bulleted slide to provide an 'Overall Assessment of the Evidence' that is intended to highlight any potentially controversial findings or assertions as well as give the Board a general sense of the overall strength of evidence relevant to the named Risk. This particular slide follows the set of slides in the risk package that describe the evidence base supporting the risk. The content of this slide addresses at a high level the following items:

1. The proportion of evidence from spaceflight vs. terrestrial settings
2. The quality of any pivotal studies or data referenced to support the risk posture (including methodology and generalizability of results)
3. The level of attention to experimental design and external validation for any animal-based evidence brought forth (guidelines found in Appendix F, Table F-4).
4. The influence of prior spaceflight experience on the assigned LxCs (i.e. we have or have not seen these issues in prior spaceflight experience or in long term health tracking).

Evidence supporting all or a part of a Risk Posture can include data or interpretation of data that is unpublished. However, if unpublished data conflicts with data or interpretation in the peer reviewed literature, the Board will assign higher strength to peer-reviewed data published in reputable journals.

The Risk Custodian Team assigns a Level of Evidence score between 1 – 4 (Strong - Speculative) in support of the LxC score assigned to each design reference mission (DRM) and displays it on the slide that documents the assumptions and dispositions for each DRM as shown in Figure 6

DRM Category	Mission Type and Duration	LxC and Risk Disposition (Ops)	LxC Drivers and Assumptions (Ops)	Risk Disposition Rationale (Ops)	LxC and Risk Disposition (LTH)	LxC Drivers and Assumptions (LTH)	Risk Disposition Rationale (LTH)
Low Earth Orbit	Short (<30 days)	*1x1 Accepted*	**Likelihood:** **Consequence:** *Example*	Rationale: Risk Posture Level of Evidence: **STRONG**		**Likelihood:** **Consequence:**	Rationale: Risk Posture Level of Evidence:
	Long (30 days to 1 year)		**Likelihood:** **Consequence:**	Rationale: Risk Posture Level of Evidence:		**Likelihood:** **Consequence:**	Rationale: Risk Posture Level of Evidence:

Figure 6: Example showing how to communicate the level of evidence that supports the risk posture for each DRM.

Level of Evidence Score

An assignment of "1" indicates a Strong level of evidence; "2" indicates a Moderate level of evidence, "3" indicates a Weak level of evidence, and "4" indicates Speculative or hypothetical level of evidence. Definitions and guidance for assigning these levels are provided in Appendix F, and are based on a subset of the Bradford Hill Criteria to ensure broad applicability across the different types of evidence relevant to human spaceflight. Given the variety of fields in which evidence is assessed, the Board does not set specific study criteria for strength of evidence but relies on a critical appraisal by the Risk Custodian Team of the literature and data as it applies to human spaceflight. The Risk Custodian Team should be prepared to respond to questions about the assignment of Level of Evidence and their assessment of the quality and applicability of specific studies and data. Where the Board feels that the evidence presented is not consistent with the recommendation from the Risk Custodian Team, the Board Chair reserves discretion to assign a different level of evidence.

Additional Considerations

Note that the basis for making a recommendation on Level of Evidence is not related to consideration of what is the 'best available' in the research and literature. Human spaceflight is a young and evolving field and the purpose of a Level of Evidence score assignment is to express the current understanding of the linkage between the Hazard(s) and claimed effects on humans that rise to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority. If the evidence base is sparse due to limited research opportunities, the Level of Evidence score assigned should be commensurate with an honest assessment of the likelihood of a clinical or operational impact.

As needed, special working groups of qualified subject matter experts are convened by the Board Chair to consolidate a position on specific aspects of evidence that require more deliberation than is warranted during an official Board meeting. Positions and recommendations made by the working group serve as additional official inputs and are presented as a separate assessment in the risk presentation package. The Board considers this pre-determined content as a means to limit the discussion of highly technical evidence at Board meetings.

The Board Chair previews these evidence assessments with the Risk Custodian Team prior to Board consideration for coherence and interpretation.

For Concerns, the limitations of the available related evidence are reviewed and used to identify high value information needed to determine if the Concern should be elevated to a Risk or Closed. The Board identifies criteria required to evaluate progress in understanding the Concern at future reviews.

Risk Custodian Teams returning for risk updates also assess whether new evidence supports any updates to existing standards and make attendant recommendations to the Board and to the Standards Team.

3.2.8 Risk Posture

The Risk Posture is an agreed upon understanding of the state of a Human System Risk decided on by the HSRB that is based on assigned DRM-specific LxC scores and their drivers and underlying assumptions, as well as associated risk colors, Risk Dispositions and rationales. It enables the HSRB to communicate the supporting assessment for the Human System Risk that the Agency and crew are likely to carry based on the best available evidence. These basic Risk Posture elements are captured in the Risk Summary and in detail as part of the risk record in the template shown in Figure 7. Updates to Risk Posture are a major product delivered by the HSRB to Board stakeholders. This Risk Posture representation is the highest level communication used to inform stakeholders of the risk landscape as it is currently understood.

Risk Posture
LxC Drivers/Assumptions - Risk Dispositions – LOE

DRM Category	Mission Type and Duration	LxC and Risk Disposition (Ops)	LxC Drivers and Assumptions (Ops)	Risk Disposition Rationale and LoE (Ops)	LxC and Risk Disposition (LTH)	LxC Drivers and Assumptions (LTH)	Risk Disposition Rationale and LoE (LTH)
Low Earth Orbit	Short (<30 days)		Likelihood: Consequence:	Rationale: Risk Posture LOE:		Likelihood: Consequence:	Rationale: Risk Posture LOE:
	Long (30 days to 1 year)		Likelihood: Consequence:	Rationale: Risk Posture LOE:		Likelihood: Consequence:	Rationale: Risk Posture LOE:

Figure 7: Risk Posture Chart in the Risk Record

The figure shows LxC information for the Ops and LTH risk impact categories per DRM with associated Risk Dispositions and Risk Disposition Rationales and LOE Score as representing the Risk Posture. A Flight Recertification risk impact category column is added in cases where it is the driver for the Risk

3.3 PLAN

The risk mitigation plan Phase is intended to inform stakeholders at a high level of what the Board considers important to effectively mitigate a Risk or investigate a Concern. The following are areas of responsibility regarding risk mitigation plans are described below.

HSRB is responsible for the following activities:

1. Identification of the framework for risk mitigation
2. Identification of the criteria by which the maximum LxC score for a particular risk would be reduced, with the expectation that the Risk Color would move from red to yellow or yellow to green
3. Identification of high- value risk mitigation targets that can be undertaken by the risk stakeholders
4. Development of relevant metrics to track progress on risk reduction efforts

Risk stakeholders develop plans and generate deliverables for reducing risk that the HSRB may review and either approves of or disapproves of based on whether those the plans and associated deliverables align

with Board expectations regarding effective risk mitigation.

3.3.1 Risk Mitigation Framework

The framework for risk mitigation includes five categories by which investments can support effective reduction of risk. Deliverables such as scientific research, occupational or clinical surveillance measures, standards, and technology transition to operations, should all contribute to one of the following categories to be considered useful for risk mitigation:

- ***Risk Characterization*** – Deliverables in this category contribute to understanding the nature of the Risk - how and why the Risk occurs – and enables plans to decrease likelihood or consequence based on that understanding. A critical part of characterization is developing an understanding of the magnitude of the impact of that risk on spaceflight crews. This helps identify when risks are worth investing in and when they should be down-prioritized in favor of other risk investments.
- ***Prevention (Hazard Control)*** – These deliverables identify ways to prevent Risks from occurring or to decrease the likelihood they will occur (e.g., crew selection recommendations, HSI recommendations, standards recommendations, clinical practice guidelines, and flight rules).
- ***Consequence Reduction*** – These deliverables identify approaches that will reduce the impact severity of a Risk that are expected to have adverse effects on crew health or on mission objectives (e.g., countermeasures development and recommendations, healthcare diagnosis and treatment capabilities, and clinical practice guidelines).
- ***System Resilience (Improve Margin)*** – These deliverables identify system improvements that may directly or indirectly improve Human System Risk posture by helping to improve crew resilience (i.e. total system margin to tolerate error or off nominal operations) in accomplishing mission objectives. System improvements such as decreased need for valuable mass, power, volume, or data storage or bandwidth requirements by technologies that enable risk mitigation in the above categories are held here. These savings increase the likelihood that risk mitigation technologies will survive system trades and be fielded. Improvements in Risk Posture for those risks dispositioned as ***Accepted with Optimization*** or ***Accepted with Monitoring*** are expected to have value for further investments from the larger human system perspective even though they may have been mitigated as individual risks.
- ***Risk Acceptance*** – Deliverables that provide information designed to support a decision regarding risk acceptance of a Risk with a maximum LxC score at a level greater than 10 (upper limit for a green LxC color) are considered here. These may include information on return on investment or cost and schedule limitations. These serve to initiate discussion about whether risk mitigation investments for the Risk in question are best moved to other areas.

3.3.2 Color Change Criteria

The Risk Custodian Team establishes criteria that define risk mitigation expected to result in lower LxC Scores that would in turn change the Risk color from red to yellow or from yellow to green for each risk. These criteria can include fundamental questions answered, demonstrations of capability or countermeasures efficacy, acceptance of new standards, or other high level targets. These are intended

to inform stakeholders of the Board's most recent high level assessment of what targets, if achieved, are likely to result in a demonstrable improvement in Risk Posture.

3.3.3 High Value Risk Mitigation Targets

Once the above risk-reduction color change criteria are established, the Risk Custodian Team identifies high -value risk mitigation targets for Board approval. These typically include areas where there are major gaps in knowledge or capability; or other targets that promise to yield returns worthy of investments in time, money and other resources by stakeholders interested in reducing Human System Risk.

3.3.4 Risk Metrics

It is important to measure progress on the likelihood and consequence for any given risk, and to effectively communicate reduction of risk based on evidence over time. Risk metrics are measures intended to communicate progress on changes in Risk Posture based on evidence over time. These are based on available data relevant to the consequence(s) that are gathered from in-flight mission medical and scientific research operations, spaceflight analogs, terrestrial analogs, astronaut health surveillance, and animal models/data correlated with medical data from NASA databases [e.g. LSAH, Life Sciences Data Archive (LSDA)], or environmental and terrestrial databases (Figure 6). This information can be a description of the measure(s) or a graphical representation of the progressive mitigations towards an acceptable level of risk. A Risk may have more than one metric. For physiologic risks, a metric should demonstrate improvement over time in either the occurrence rate or the consequence severity as supported by evidence. For example, potential Renal Stone Risk metrics may be: (1) a reduction in the number of kidney stones occurring in crewmembers; and (2) the characteristic time that a crewmember may be incapacitated due to improved treatment of kidney stone symptoms. These metrics are proposed by the Risk Custodian Team at periodic risk updates and approved by the Board. If the Risk Custodian Team is not able to identify at least one implementable metric, then candidate metrics can be proposed with a forward path for data collection that will enable the development of an effective metric.

3.3.5 Risk Mitigation Plans

Stakeholders manage and implement plans for risk mitigation and are invited to provide information on deliverables, funding levels and schedule relevant to mitigation of each given risk when risk updates are being considered at the HSRB. The risk stakeholders could be operational personnel from the Space Medicine Operations Division to provide insight for strategic mitigation planning and ensure operational consideration and deployment, Element Scientists from HRP who have research mapped to the HSRB risks, representatives from CHS who describe occupational surveillance or evidence activities relevant to characterization of evolving Risk Posture, or representatives from the Habitation – CHP SCLT who describe roadmap deliverables relevant to system maturation and risk mitigation.

The HSRB considers these risk-mitigation plans in the context of the agreed -upon risk mitigation color change criteria and ranking of high value risk -mitigation targets, and either approves of or disapproves

of these plans. Any disapproval is discussed with the management group of the stakeholders to improve communication about what changes in the plan should be considered for effectively reducing risk to crews and to provide feedback on whether such changes would be likely to receive approval from the Board.

3.3.6 Concern Investigation Plan

The approach to each Concern is to target either elevation to a full Risk or closure. The primary effort seeks to gather available evidence and assess whether the Concern represents a true risk to crews and warrants elevation or if the impact to crew health and performance is likely to be negligible and warrants closure. Stakeholders with investments relevant to a Concern are invited as well to provide information on deliverables that could inform Board disposition of the Concern and request approval.

3.4 REVIEW BY HSRB AND DECISIONS

When the package for a risk update or proposal for a new Risk or Concern is prepared, it is presented by the Risk Custodian Team to the HSRB. If the content contains Sensitive But Unclassified (SBU) as defined in *Sensitive But Unclassified (SBU) Controlled Information* (NID 1600.55) data, the Risk package may be available to a limited audience. The HSRB decides whether to release the package via the Change Request (CR) process of HHPD's Configuration Management (CM) system. If the board decides not to release the CR, they must provide the Risk Custodian Team with specific actions that will allow the CR release.

Once open, the CR process receives comments from mandatory and optional evaluators, and accommodates discussion between the evaluators and the Risk Custodian Team to disposition the comments as facilitated by the HSRB Risk Management Office. A package is brought back to the Board that highlights the final changes for approval or discussion in the case of non-concurrence or dissent.

The HSRB Chair, with assistance from the Board, assesses the inputs derived from the Identify, Analyze and Plan phases and makes informed, timely, and effective decisions consistent with those responsibilities listed in Figure 3 and the *HSRB Charter* (SA-CHT-02). Decisions are captured in the minutes of the Board for formal archiving. Formal dissents may be brought forward by anyone who would like the Board to reconsider decisions in light of additional information that was not present when previously made. These dissents shall be elevated to the OCHMO Level 1 board per the process documented in the *NASA Governance and Strategic Management Handbook* (NPD 1000.0) and the *NASA Space Flight Program and Project Management Requirements* (NPR 7120.5). The following section lists the specific decisions made by the HSRB Chair for the different items that come to the Board:

3.4.1 Proposed Concerns

The HSRB decisions for proposed Concerns are ***Baseline as Concern*** or ***Disapprove***. The Board may decide to approve a Concern with a plan of action to investigate the topic and a return to the Board for the next decision.

3.4.2 Returning Concerns

The HSRB decisions for returning Concerns are ***Elevate to Risk***, ***Close Concern, or Continue Evaluation.*** If the evidence brought forward by the Risk Custodian is sufficient to support the case for a Risk, including an LxC assessment and the minimum set of information for a risk record, the Board may decide to elevate the Concern into a Risk. In those cases, the Board may issue an action to further develop the Risk Posture package and write-up. The Board may decide that the Concern shall be closed if it is deemed that the magnitude of the concern is insufficient to warrant elevation to a Risk. The Board may recommend that continued evaluation of the Concern is needed if the update has not identified sufficient evidence to characterize the magnitude of the concern.

3.4.3 Proposed Risks

The HSRB decisions for proposed Risks are ***Baseline as Risk*** or ***Disapprove***. The Board may decide to baseline a new Risk based on the strength of the evidence base brought forward. Newly baselined Risks receive an initial disposition of ***Requires Characterization*** or ***Requires Mitigation*** for at least one DRM category.

3.4.4 Returning Risks

The HSRB decisions for returning Risks are ***Approve Risk Update*** or ***Disapprove Risk Update*** as proposed. In the case of disapproval, the Board will give instruction as to which parts of the update require revision.

When stakeholders bring forward risk mitigation plans for evaluation, the Board can ***Approve*** or ***Disapprove*** these plans as consistent or not consistent with the HSRB understanding of effective risk mitigation needs.

The ultimate product developed by the HSRB is the approved Risk Posture for each Risk along with a narrative risk Executive Summary describing that Risk Posture at a high level. These products are part of each risk record developed from the CR package including post-CR inputs and archived in the HSRB risk database/tool that is made available to internal NASA stakeholders. For decisions that are risk neutral or that improve the Risk Posture, the HSRB makes decisions and engages in quarterly updates to the CHMO for awareness. For decisions that accept more risk on behalf of the government or which represent significant changes to red or critical risks, board decisions will be brought forward for concurrence from the CHMO. Occasionally, the Chair may recommend communication of specific Human System Risk findings to a spaceflight programs' Chief Health and Performance Officers.

At any time during these deliberations, the HSRB Chair, on behalf of the HSRB members, may issue related actions as needed with a clearly assigned responsible actionee and return date. The execution of these activities will be managed by the designated actionees and tracked by the HSRB Risk Management Office.

3.5 TRACK/IMPLEMENT

In this phase, the execution of the risk mitigation plans as approved by the Board is tracked by the HSRB Risk Management Office and the Risk Custodian Teams to inform the next risk update. To facilitate this process, the Risk Custodian Team identifies and recommends for approval by the HSRB, at least one relevant risk metric to monitor. The Board may request updates on relevant deliverables or timely data updates as needed to track progress.

In general, the Board will plan to review Risks that are red in at least one DRM category on an annual basis and Risks that are yellow in any DRM category at least every two years. Event-driven updates and other timely data presentations may occur more frequently as needed.

The HSRB Risk Management Office manages the risk workflow process relevant to any scheduled risk update.

Risk Workflow

Figure 8 shows the risk workflow process that guides a Risk Custodian Team through a risk update. It begins with a Risk Custodian Team orientation meeting with the Risk Manager to agree on the deliverables and a schedule for the update.

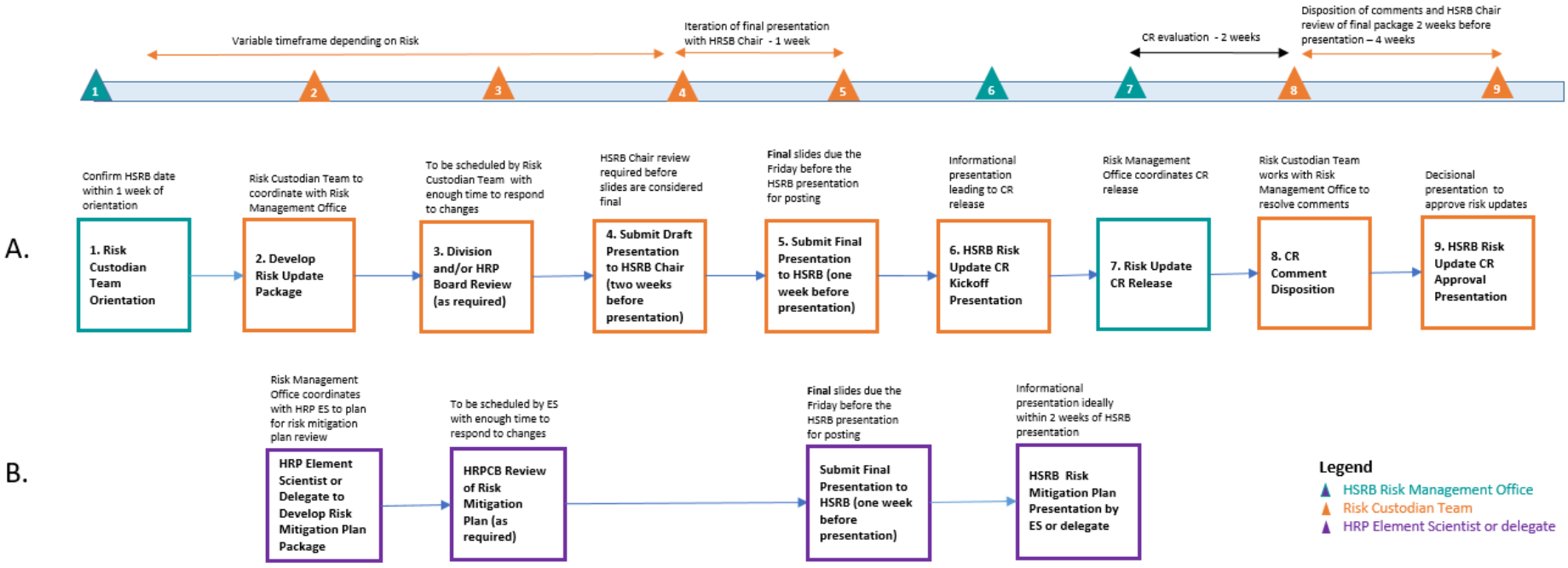

Figure 8: Risk Workflow for the Risk Update Process

This figure shows the workflow for (A) Risk Custodian Teams and (B) An example stakeholder (HRP) where an HRP Element Scientist provides insight regarding deliverables relevant to risk reduction in close proximity to the HSRB CR process.

The workflow process was developed and is tracked to ensure timely delivery of materials and to provide sufficient lead time for appropriate vetting by the HSRB Risk Management Office prior to initial presentation at the HSRB. Risk Custodian Teams often have competing priorities and the HSRB Risk Management Office works with the respective HH&P Divisions to ensure appropriate prioritization of the risk updates as needed.

The process includes the concurrent flow for invited delegates of risk stakeholders that own mitigation plans to provide insight into funded activities and deliverables, high level cost and schedule, and expected return on investment.

The HSRB will not review research data until it has been vetted through the funding authority prior to presentation at the HSRB. Any other HH&P Division control board or NASA vetting of the risk package is not required by the HSRB and is determined by the Risk Custodian Team members' Divisions.

The status of other risk-related items that contribute to risk mitigation is tracked by the HSRB Risk Management Office - for example, relevant new standards and standards updates that have come through the HSRB, and Human System Risk items ready to enter or are within the Transition to Operations (TtO), Tests of Technologies and Procedures (TTP), and Medical Technology Evaluation Demo (MEDTED) processes (See Appendix E). The Board may request updates on the progress of these items as they may signal a change to Risk Posture.

The HSRB Risk Management Office also tracks actions associated with risks and may request current actionees of selected relevant actions for periodic updates to the Board.

Configuration Management Process

At the end of the risk update and review process, the CR must be closed by the Board in a timely fashion to enable continuation of the CRM process. This section is intended to provide context and Board expectations regarding the CR process referenced in Section 3.4.

When risk updates come before the HSRB, a package is released for CR evaluation. Over a two week period, mandatory and optional reviewers have the opportunity to provide feedback on the risk package. Depending on the size of the package, the CR deadline for comments may be extended. Mandatory reviewers will get the allotted timeframe for response. They will then receive two email follow ups for comments if they have not provided input by the time the comment period has ended. *After the two email follow ups the open CR will be triggered to return to the board at the earliest opportunity* on the schedule for closure. At that closure *if any Mandatory reviewers have not provided input they will be asked if they have any specific objections to closing the CR. If there are specific concerns the board will address them in real time to enable closure of the CR.*

If a Mandatory reviewer states that they have not had adequate time to review the CR (or they or their alternate are not present at the board meeting*), an automatic action will be created for that Mandatory reviewer to provide input within 1 week*. *If they still have not provided input at the close of the action timeframe, then the Mandatory reviewer will be marked as 'No Eval Submitted' Mandatory evaluator was non-responsive.*

All reviewers are expected to provide comments in the *From:* and *To:* format in the accompanying

evaluation spreadsheet provided and rationale for change so that Risk Custodian Teams have sufficient information to understand and evaluate the input. Any comments that do not include a ***To:*** response portion will be rejected for lack of actionable information.

All reviewers will be contacted by email with the Risk Custodian Team's disposition of their comments and will have one week to respond to those dispositions. Reviewers who feel that the disposition of their comments is inadequate are expected to respond to the email and inform the Risk Custodian Team and HSRB Risk Management Office whether a face-to-face discussion is preferred for resolution. If after the meeting no resolution is reached, the Risk Custodian Team brings forward the comment in question at its CR decisional presentation, and requests the Board for a decision. Formal dissents will be handled according to the process described in Section 3.4.

3.6 DOCUMENT AND COMMUNICATE

A continuous process of documentation, tracking, and communication of Human System Risk baselines, statuses, and updates is carried out via the HHP CM system described in the *Configuration Management Plan – Human Health and Performance Directorate* (JSC 28330). The CM process is applied to the management of CRs, Board agendas, presentations, minutes, action items, and directives. This information is presented within the HSRB Dashboard which is part of the HHPD Dashboard. The amount of content of HSRB decisional packages is managed by the presenters such that presentations can be made within reasonable time to allow adequate time for discussion by the Board (40 minutes for risk update presentations, 20 minutes for TtO and standards approval presentations). Exceptions to this will be granted on a case by case basis.

The CR-processed and approved Risk/Concern information is archived in a risk record that contains the written Executive Summary, status of Risk Posture, summary of the evidence base that supports the Risk Posture, recommended mitigations, and a bibliography/references section that supports the evidence content. Fundamental risk information is summarized in a Risk Summary record. The risk records are archived within the HSRB risk database/tool (also linked from the HSRB Dashboard) which is internally available to the HSRB stakeholder community. This database tracks all Risk/Concern updates including previous versions of the risk records as well as retired Risks and closed Concerns.

The HSRB Chair communicates relevant risk information to the HSRB members, personnel in relevant programs, HHPD and other directorates, and reports this information to the OCHMO through quarterly updates and routine communications.

Regular informational sessions targeted towards Risk Custodian Teams are organized by the HSRB Risk Management Office to increase and sustain engagement in the risk management process. This includes periodic educational sessions that allow information exchange regarding the evolution of processes and that encourage feedback on potential improvements. The *Don't Panic: A Risk Custodian's Handbook for the Human System Risk Board* (SA-HDBK-01) is updated as needed to enable a non-jargon based understanding of the knowledge that new Risk Custodian Teams or team members need to effectively participate in the risk process.

The HSRB Risk Management Office seeks to take advantage of software and computational advances

that enable better tracking and reporting on risk. It screens and works to incorporate organizational and relational approaches that can improve the ability and efficiency of Risk Custodian Teams to identify, interpret, communicate and archive information relevant to a given risk including evidence and deliverables from stakeholders. It also seeks to identify and implement approaches that improve Board insight into the links between Human System Risks and the appropriate prioritization of those risks to improve Board decision making and effectiveness of communication.

3.7 PROGRAM RISK INTEGRATION/LxC MAPPING TO PROGRAMS

As part of HMTA functions, the HSRB and HSRB Risk Management Office hold a responsibility to communicate, where appropriate, Human System Risk information to new and existing spaceflight programs through their HMTA Chief Health and Performance Officers for consideration by their risk boards. The HSRB Risk Management Office interfaces with the HMTA and the Chief Health and Performance Officers to develop a process for enabling this communication and awareness of programmatic overlaps with tracked Human System Risks.

3.8 RISK PRIORITIZATION

With around 30 Human System Risks (Appendix C), it can be difficult to gain insight into which Risks are the highest priority in a changing risk landscape. The development of criteria to transparently prioritize risks in a repeatable manner is critical for HSRB stakeholders when considering allocation of resources and return on investment. The principles articulated below represent our best understanding of the prioritization drivers that should inform risk prioritization at the HSRB.

3.8.1 Risk Hierarchy

The concept of risk hierarchy is communicated by rating risks on a scale that ranges from foundational (level 0) to dependent (level 5). Foundational Risks are those that can become contributing risk factors for other Risks that are dependent on them. Figure 9 shows the hierarchy framework identifying conceptually distinct categories that denote levels at which Human System Risks impact crews and programs. The hierarchy is a pyramid structure identifying the levels of risk that are expected to contribute to Loss of Mission (LOM), Loss of Crew (LOC), and Loss of Mission Objectives (LOMO) when inadequately mitigated. This framework is based on the objectives hierarchy model described in the *NASA Risk Management Handbook* (NASA-SP-2011-3422) and tailored to be meaningful for categorization of and relationship mapping between/among Human System Risks.

3.8.1.1 Hierarchy Categories and Definitions

Risks that are best described by the more foundational categories are likely to have compounding, and in some cases, potentially synergistic effects on the Risks in higher level categories. For example, if the *Food-Nutrition Risk* and the *Sleep Risk* that belong to the *Basic Human Needs* level (level 1) are inadequately mitigated, it is likely that dependent performance-focused Risks such as *BMed Risk* higher in the pyramid (*Human and Vehicle Maintenance-Level 3*) will fail to be mitigated as well. In this sense, foundational Risks must be addressed to ensure that more dependent Risks are able to be mitigated.

This also identifies the manner in which system resilience in Human System Risk mitigation can be identified and approached. Although Risks such as *Food-Nutrition*, *Sleep*, or *Aerobic Capacity* may be yellow or green based on a focused approach to that specific need, improvements or optimization at foundational levels are expected to provide increasing dividends for the mitigation of more dependent risks. This enables stakeholders to evaluate whether investments in further risk mitigation of a Risk with a current yellow or green Risk color are warranted from the larger system perspective.

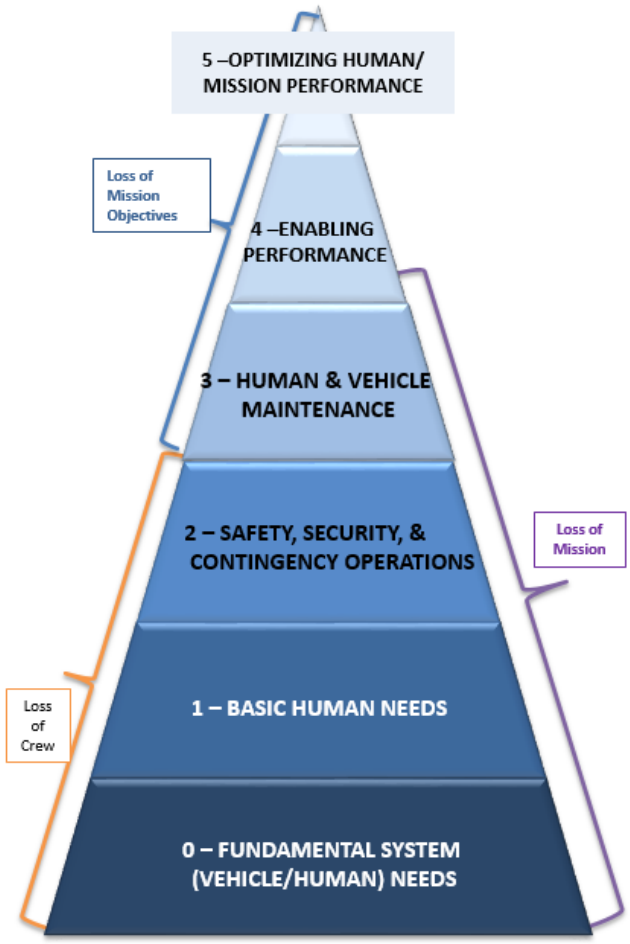

Figure 9: Notional Human System Risk Objectives Hierarchy

The hierarchy categories are listed in order from most fundamental (0) to most dependent (5).

0 – Fundamental System (Vehicle/Human) Needs – This level describes the system needs of the vehicles that must be considered from the beginning of the design process. Changes to these considerations late in the design process are likely to incur additional cost and risk to program schedules. This affects Human System Risks because cost and schedule pressures often drive programs to 'accept' additional risk through not fully addressing Human System needs in the final vehicle design. This category is critical

to ensuring that Human System Risks maintain visibility of their contributions to a much larger system of risk. Insufficient risk mitigation at this level will impact human health and performance and can result in LOC, LOMO, and LOM.

Examples of technical standards that address this level of risk include but are not limited to: Launch System - cryogenic, tanks, engines, boosters, avionics, and software. Capsule/habitat - pressurized volume - DCS prevention (incl. LEA Suits, EVA atmospheres), human data set – anthropometrics & strength, occupant protection, avionics, software, abort system. Landing - heat shield, parachutes, vehicle control recovery. Emergency Egress Capabilities.

Examples of known risk mitigations dependent on early vehicle design consideration are for the following Risks: *Bone, Muscle, Aerobic Risks* – exercise systems including devices, adequate space for use, and vibration isolation systems; *Sleep Risk* – private crew quarters, local environment control; *Food-Nutrition, Pharm Risks* – food system, refrigeration, inventory capabilities; *Medical Conditions Risk* – integrated data systems, diagnostic and treatment hardware and software; *CO_2, Toxic Exposure Risks* - environment control, atmospheric monitors with data logging and downlink capability; *HSIA Risk* – system maintainability, reparability, habitable volume, displays, software, decision support, autonomy; *Dynamic Loads Risk* – seat and restraint design, vehicle acceleration and load monitoring, crew video; *Radiation Risk* – shielding and reconfigurable mass, radiation monitors with data logging and downlink capability; *Dust Risk* – filtration and particulate exclusion, dust/particulate atmospheric monitoring with data logging and downlink capability.

1 – Basic Human Needs – Human systems carry significant risk if basic human needs are not met because of insufficient consideration given to them in the design of the vehicle and mission trade space. Inability to provide sufficient food, nutrition and hydration, sleep, breathable atmosphere, etc. will impact both crew health as well as their ability to perform and achieve mission objectives. Insufficient risk mitigation at this level will impact human health and performance of crews and can result in LOC, LOMO, or LOM.

Examples of standards that address this level of risk include but are not limited to: life support standards such as temperature, air (O2, CO2 levels), acoustic; sleep standards; minimum hydration & nutrition standards; waste disposal standards; cleanliness and personal hygiene standards; and lighting standards.

2 – Safety, Security and Vehicle Operations – Risks associated with safety and emergency response apply after the level of basic human needs have been met. Both crew and spacecraft are dependent on human capability for anomaly identification and response, whether a medical issue with a crewmember or an anomaly in an engineering system. Examples can include the risks of crew inability to egress a vehicle in an off-nominal landing, whether due to deconditioning or to poor design choices. Insufficient risk mitigation at this level will impact human health and performance of crews and can result in loss of individual crew life (LOCL), LOC, LOM, or LOMO.

Examples of standards that address this level of risk include but are not limited to: baseline medical care standards; vehicle design/volume and operation; electrical shock and touch temperature standards; toxicology/materials standards; hatches; pressure equalization and control standards; alarms, displays, usability and error analysis standards; crew performance and training for vehicle operations; translation paths; inventory management; contingency operations; and radiation SPE protection standards.

3 – Human and Vehicle Maintenance – Health maintenance is possible once basic needs and safety have been addressed. Vehicle maintenance required by the crew assumes a basic level of crew wellbeing sufficient to perform maintenance tasks as well as sufficient Human Systems Integration in the design process to enable crew to perform any needed maintenance activities at the level demanded by the mission type. In the case of missions with significant communication delays, this means that HSI anticipates crew ability to identify and respond to anomalies independently of mission control expertise for as long as needed. Aspects of both physical and mental health are considered as part of mission concepts to provide prevention, diagnosis, treatment, and reconditioning capability appropriately scoped to the mission at hand. Physical and cognitive ability to perform all maintenance tasks are considered at this level. Risk mitigation may include considerations early in vehicle (or suit) design as well as adjustments that can be made late in design. Insufficient risk mitigation at this level will impact human health and performance of crews and can result in LOCL, LOC, LOM, or LOMO.

Examples of standards that address this level of risk include but are not limited to: nominal vehicle maintenance/interaction with human standards; medical care maintenance standards; human health countermeasures standards; social well-being standards; privacy and family communication standards; team dynamics standards; and circadian lighting standards.

4 – Enabling Performance – Enabling performance recognizes that specific missions may demand levels of human performance that are beyond what is typically considered in ISS type missions that the agency has optimized over the last 20 years. For example, current assumptions about readiness and fitness for EVAs are generally based on the experience of the ISS where EVAs are a periodic occurrence, have a long pre-breathe to protect health, and demand a level of fitness commensurate with suit mobility challenges in microgravity. For future Lunar surface EVAs these assumptions will underestimate the amount of time and resources needed and level of fitness required to perform multiple EVAs on a celestial surface with greater frequency than is demanded by the current ISS schedules. To enable performance, vehicle and mission managers must include the set of monitoring and interventions needed to keep crew performance within an acceptable range for mission objectives. Mission performance goals should be considered after maintenance issues for crew and vehicle health have been addressed. Physical and cognitive ability to perform complex tasks beyond maintenance are held at this level. Risk mitigation may include considerations early in vehicle design as well as adjustments that can be made late in design. Insufficient risk mitigation at this level will impact human health and performance of crews and can result in LOC when related to crew performance of safety and emergency tasks but more likely LOMO or negative impacts to crew time or resources needed by crew.

Examples of technical standards that need to be in place and decomposed into requirements for SRR include but are not limited to: fitness for duty standards; human performance standards; habitable volume standards for non-vehicle operations that support mission objectives not related to safety & security (science, non-critical mission objectives); and training and vehicle system design to minimize resources.

5 – Optimizing Human/Mission Performance – Optimizing human/mission performance is possible once baseline performance capabilities have been established and after addressing health maintenance, training, and systems design. Appropriate levels of physical and cognitive ability are maintained to

perform multiple complex tasks throughout expected degradation from prolonged exposure to the spaceflight environment. Insufficient risk mitigation at this level is most likely to result in negative impacts to crew time and resources. It may not result in LOMO in a short duration mission but may contribute to LOMO in longer duration missions as the effects of various risks stack and system margin is expended in unexpected places. Risk mitigation may include considerations changes made early in vehicle design as well as adjustments that can be made late in design or during operations and are intended to positively impact crew-time availability through crew efficiency.

Examples of recommendations that address this level of risk include but are not limited to: sending fresh fruit and care packages to the ISS to mitigate *Food-Nutrition* and *BMed Risks*; advanced tools for training and task design; and crew self-scheduling capabilities. These are countermeasures that improve crew time and resource efficiency and improve Human System resilience.

3.8.1.2 Hierarchy Category Risk Mapping

Within the Risk Objectives Hierarchy, each Risk is book-kept in a primary level with secondary level categorization that describes known impacts to other levels of the hierarchy. The criteria for primary and secondary assignment are described below:

Primary Criteria – These criteria refer to the bases that determine the level at which a Risk is tracked within the Risk Objectives Hierarchy. A Risk will be placed in that primary level if the scenario in the Risk Statement is primarily related to the functions described in the level definitions above. Other categories that are impacted by the risk countermeasures or contributing factors are considered by secondary criteria. The Primary mapping for risks is used in the creation of DAGs discussed in Appendix G.

Secondary Criteria – There are two options for categorizing a risk as having secondary criteria in the Risk Objectives Hierarchy described below:

- Known dependence - A Risk primarily held at one level may impact the overall status of crew function as described in other levels because of inadequate risk mitigation in the primary level. For instance, if behavioral health of the crewmembers (for the *BMed Risk*) is not maintained (level 3 – *Human and Vehicle Maintenance*), then crew performance is likely to be negatively impacted as well (level 4 – *Enabling Performance*). This is illustrated by the blue marked areas above *BMed Risk* in level 3 in Figure 10. If either physical or cognitive capabilities are not satisfactory, then crew response to safety events may be compromised (level 2 – *Safety, Security and Vehicle Operations*). This is illustrated by the blue marked areas below *BMed Risk* in level 3 in Figure 10.
- Fundamental System Impact - A Risk that requires early consideration in the engineering life-cycle for effective mitigation (level 0 – *Fundamental System (Vehicle/Human) Needs*) should be supported by rationale. For instance, food (for *Food-Nutrition Risk*) may require refrigeration or muscle/aerobic/bone (For *Muscle/Aerobic/Bone Risks*) may depend on exercise hardware and software that will incur significant cost if considered too late in the design process of the vehicle. These are the green marked areas corresponding to level 0 for these risks in Figure 10.

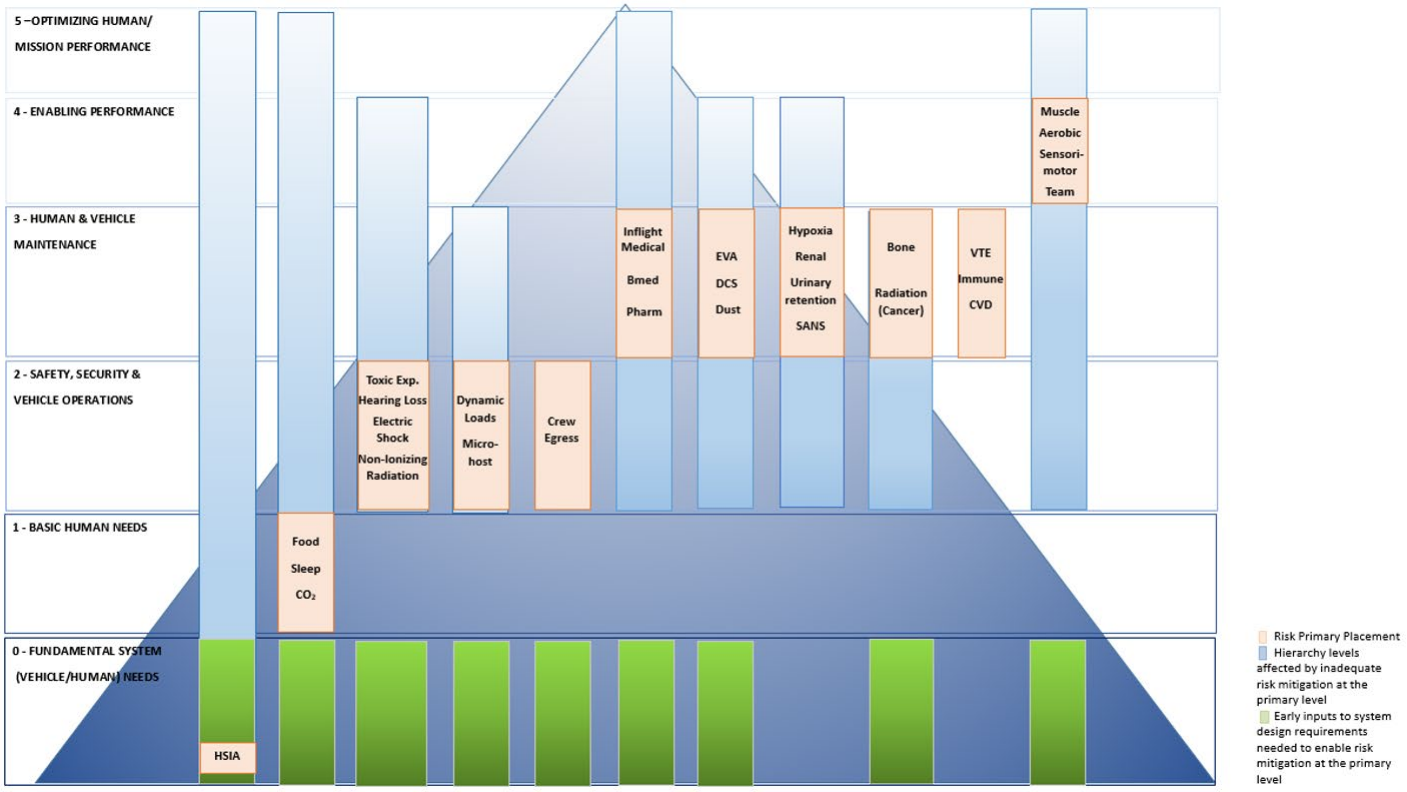

Figure 10: Risk Mapping to Notional Objectives Hierarchy

Risks are mapped to the Notional Objectives Hierarchy at a primary level of expected risk consequence. This example case shows a notional graphical representation of that mapping with secondary criteria illustrated. Secondary criteria show what other levels of the hierarchy are affected by inadequate risk mitigation at the primary level (blue boxes) and which risks have known mitigations that depend on mature system requirements being articulated and provided to the System Requirements Review for any spaceflight program (green boxes in Level 0). This mapping is expected to dynamically change as new evidence becomes available and risk categorization is updated.

3.8.2 Risk Dependencies

In the operational world of spaceflight, the impact of these Risks will be felt in a cumulative manner by the crew and mission and not in siloes as they are book-kept by the HSRB. As such, interactions between Risks exist beyond the dependency framework shown in Figure 10. There is value to identifying and mapping those relationships as they become known. There are different facets to the synergistic effects that Risks share. In certain cases, some Risks are influenced by overlapping contributing factors, may be informed by common metric measures, may be mitigated by the same standards, or may be mitigated by common countermeasures. The HSRB attempts to assess these known interdependencies in part using the Risk Objectives Hierarchy and prioritizes Risks with higher levels of expected interactions with other Risks over those that have less interdependency.

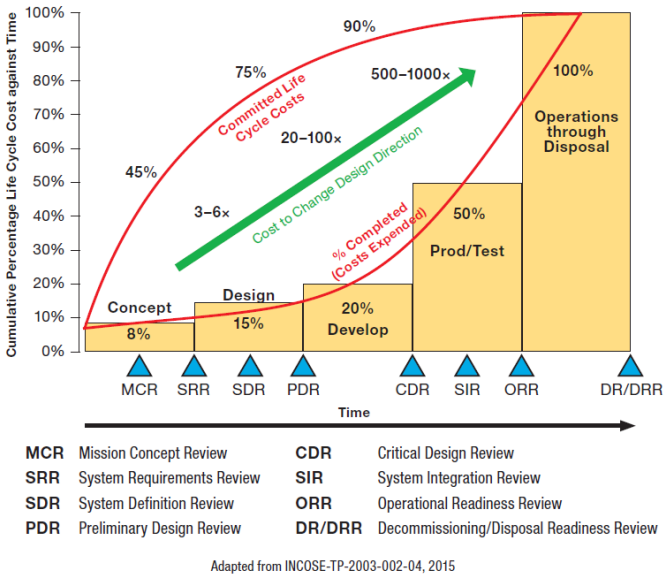

Figure 11: Life Cycle Costs In the Life Cycle

This picture showing how life cycle costs are locked in, is taken from the book Engineering, Life Sciences, and Health/Medicine Synergy in Aerospace Human Systems Integration: The Rosetta Stone Project.[2]

As an example, Figure 11 shows how effective risk mitigation for Human System Risks depends on effective HSI architecture and processes beginning in the earliest phases of the engineering life cycle. The hypothesis is that early intervention (through effective human system integration processes) results in decreased total life cycle costs to the program and minimized risk. Each of the risk mitigations required for any of the other Human Systems Risks must be expressed in the vehicle systems in order to realize risk reduction. Cost and schedule delays are examples of programmatic risks that are experienced when this is not done, but this also results in increased Human System Risk through programmatic pressure for waivers or exceptions to inadequate designs or failed verifications late in the program life cycle. Program resistance to appropriate fixes occur late in the program life cycle and are often due to cost and schedule delays. These result in increased Human System Risk because the human crews are viewed as more flexible and able to absorb or compensate for inadequate designs. Each programmatic decision made independently to shift risk to the human system ultimately gets stacked and expressed in operations during a mission. Risks that require mitigation considerations through fundamental system design need to be addressed through provision of mature requirements before the System Requirements Review. If they are not considered until later the Agency will be forced to choose between significant cost and schedule impacts or a higher level of risk acceptance.

The HSRB Risk Management Office seeks and implements both software and data approaches that enable the documentation and visualization of known and suspected Risk-Risk interdependencies that are likely to improve board insight and enable improved quantification of Human System Risk effects. A format for a graphical representation of linkages and interactions between contributing factors, risk scenario elements and countermeasures is provided by Directed Acyclic Graphs (DAGs) and tracked by a relational database managed by the Risk Management Office. Risk Custodian Team inputs including

DAGs are included as part of the standard risk update package and the HSRB Risk Management Office works to integrate these into a cross risk framework with common language to improve the understanding and communication of Risk Posture. Where known, the Board seeks to leverage Risk-Risk interactions to better identify where investments are likely to improve overall human system resilience.

3.8.3 Risk Prioritization Score

The overall severity of Risks is communicated by risk colors at the highest levels. However for the purpose of prioritization, the prioritization (LxC) scores identify level of urgency for resolution of the risk as compared to other risks in terms of likelihood and consequence assessment. This is described in section 3.2.4 above.

3.8.4 Need Timeframe

Different Risks will be impacted by input to mission design at different points in the engineering life cycle of a program. This drives a need for some risk mitigations to be realized on program timeframes that may vary from immediate to potentially a decade of lead time. Risk mitigations that are needed sooner for program impact are prioritized over risk mitigation timeframes that have a later need date.

3.8.5 In-Mission vs. Long Term Health

Crews bear many Risks in human spaceflight. While it is a strong concern of the community to minimize the post-flight effects both in-career and post-career, it is incumbent on the Agency to prioritize in-mission Risks over long-term health Risks to crews. Crews flying on the Space Shuttle accepted a 1:90 Risk of loss of life at the end of the program, and the understood Risks were as high as 1:10 in the early phases of the program. The goal of risk management by NASA is to enable human spaceflight in the best Risk Posture we can achieve. If long term health concerns over-ride in-mission concerns then we would never fly crews.

3.8.6 Expected Investment Benefit

Terrestrial markets and industries often invest in software and technologies that may decrease our Risk Posture as capability development matures to an implementable level. This does not apply to all Risks as the unique nature of spaceflight often requires custom countermeasures that will not be addressed by terrestrial priorities or markets. For NASA risk mitigation approaches, resources should be prioritized towards those areas where spaceflight-specific challenges addressed by NASA investments can drive risk mitigation more effectively than terrestrial advances can. In risk arenas where terrestrial investments are likely to advance risk mitigation faster or more successfully than NASA specific investments, those Risks should be down-prioritized.

Using these principles, the HSRB Risk Management Office will seek to develop a transparent and repeatable method to prioritize Risks on the basis of DRMs, known or suspected Risk-Risk interactions, and to identify where the highest value investments in risk mitigation are likely to be for future exploration missions. This plan will provide insight to programs based on their most relevant DRMs into

appropriate prioritization of the Human System Risks for their purposes.

APPENDIX A: DEFINITIONS OF KEY TERMS

The following is a set of definitions for commonly used words or phrases used within the risk process managed by the Human System Risk Board. These definitions are officially accepted for purposes of HSRB applications and discussion to minimize confusion that might come from varying interpretations and historical use of the terms within and outside of NASA.

Acceptance - Agreement by the appropriate NASA management official to the change in the level of risk to programs, hardware and personnel and taking the responsibility for the potential outcome of any increase in risk.

Adjudication - The process that encompasses the process of review, concurrence, and approval of a request for relief from an Agency-wide HMTA standard. The process includes the approval or disapproval of the request by the Chief Health and Medical Officer (or delegated approval authority) and acceptance or rejection of the change in risk and acceptance of the new risk level by the appropriate NASA management official. A request is adjudicated when all steps in the process are complete.

Approval - Decision by the HMTA that a program and projects position, issue resolution, waiver to, exception to, or deviation from HMTA policy, standards or derived requirement is within NASA policy and may be implemented after the appropriate NASA management official accepts the risk.

Chief Medical Officer - A physician assigned to designated NASA Centers by the Agency Chief Health and Medical Officer (CHMO) who serves as the delegated Health and Medical Technical Authority (HMTA) for that Center.

(Concern) Closure – the decision made by the HSRB to remove a Concern from further consideration by the Board when the Concern is found to have insufficient supporting evidence for being elevated to a Risk.

Concurrence - A documented agreement by a management official that a proposed course of action associated to a program or project position, issue resolution, waiver to, exception to, or deviation from HMTA policy, standards or derived requirements is acceptable.

Consequence (C) – a possible crew health and performance outcome for a given risk. When communicating the Risk Posture, the likelihood and expected severity of each consequence is typically reported in terms of a measure of central tendency (mean or median)..

Contributing Factor – an operational, design, or human-system variable (including spaceflight hazards) that can influence the likelihood and/or consequence of Human System Risks. For example, (degree of) crew autonomy is a contributing factor to the Risk of team performance and behavioral decrements; (amount of) in-flight exercise capability is a contributing factor to Risk of reduced muscle size and strength.

The contributing factors listed in the Risk Summary could include those that remain to be proven and that are intended to be investigated.

Countermeasure – any action, hardware/software or capability provided pre-, in-, or post-mission that serves to reduce risk within the Risk Impact Categories. There are three types of countermeasures as applied to Human System Risks managed by the HSRB:

- **Monitoring Countermeasure** – a countermeasure implemented during the course of a mission

used either operationally or for occupational surveillance to provide actionable information to crew or clinicians on prevention effectiveness, and when to implement risk reduction interventions. For example, X is a monitoring countermeasure for the Risk of Y

- **Prevention Countermeasure** – a countermeasure implemented pre-flight and during flight that decrease the influence of contributing factors and hazards on the Risk or on the scenario that enables the Risk to manifest. For example, X is a prevention countermeasure for the Risk of Y
- **Intervention Countermeasure** – a countermeasure applied after the risk scenario occurs intended to reduce the severity of the consequence. For example, X is a prevention countermeasure for the Risk of Y

The countermeasures listed in the Risk Summary could include those that remain to be proven and that are intended to be investigated.

Delegation - The official process for assigning Technical Authority to a named individual and communication that delegation to appropriate community.

Design Reference Mission (DRM) – one of several proposed NASA missions, loosely defined by destination, operating environment, and expected duration used in lieu of constantly changing proposed missions.

Dissenting Opinion - A Dissenting Opinion is a disagreement with a program/project technical decision or action that an individual believes to be of sufficient importance that it warrants a specific review and decision by higher-level management.

Evidence - the information gathered from in-mission medical and research operations, performance outcomes, spaceflight analogs, terrestrial analogs, animal models, mathematical models, simulation results, medical data from NASA databases (e.g. LSAH, LSDA), environmental and terrestrial databases, or publications.

Hazard – a feature of the spaceflight environment that increases the risk of adverse health or performance outcomes. There are five spaceflight hazards that lead to Human System Risks: Altered gravity; Radiation; Distance from Earth; Isolation; Hostile Closed Environment.

Health - Individual's medical and psychological wellbeing.

Human Performance - The capabilities and needs of the human defined by physical, cognitive and psychological traits that are applied to the design of vehicles and operational tasks to achieve mission success as captured in NASA STD 3001 V1-2.

Human System - The human's capabilities and needs when considered in a consistent, methodical fashion programmatically on an equal footing to other systems in a given architecture.

Human System Concern - a potential Human System Risk for which there is insufficient evidence to allow an LxC assessment for any DRM. A Human System Concern can be redefined as a Human System Risk once sufficient evidence is gathered and to develop a corresponding LxC matrix and other required Risk information.

Human System Disciplines - The family of human-related clinical, technical and scientific disciplines

closely associated with the performance capabilities and needs of the human (e.g. clinical medicine, nutrition, toxicology, physical performance, cognitive abilities, human factors, microbiology, health physics, etc.) as captured in NASA STD 3001 V1-2.

Human System Integration – The definition of Human System Integration for NASA is still being worked within the community of practice. Until the release a different definition, the HSRB will use the following:

> HSI is an interdisciplinary integration of the human as an element of the system to ensure that the human and software/hardware components cooperate, coordinate, and communicate effectively to perform a specific function or mission successfully. HSI does this through lifecycle process inclusion of technical disciplines and domains, providing a capability that ensures the limitations and abilities of humans are adequately addressed in the final design.

Human System Risk - a recognized potential NASA space flight crew health or performance outcome that has a defined consequence and associated likelihood supported by evidence for a given DRM.

Likelihood (L) - the quantitative probability or qualitative assessment of the probability of a consequence. Each consequence can have its own associated DRM-specific likelihood.

Loss of Crew (LOC) – loss of (the whole) crew - usually reserved for catastrophic events like Challenger, Columbia, Apollo 1 but can describe an entire crew being permanently incapacitated.

Loss of Crew Life (LOCL) – loss of (a single) crew life – e.g. if Fred Haise had died of sepsis during Apollo 13 and he was the only one who died.

Loss of Mission (LOM) – indicates anything that can lead to loss of a mission – e.g. evacuation prior to mission objectives being accomplished without losing the crew as in Apollo 13 case.

Loss of Mission Objectives (LOMO) – indicates only some mission objectives may be lost and other mission objectives can still be achieved. Single crewmember disability can lead to LOMO or possibly LOM if the decreased functionality of that crewmember ends up driving an abort or if the rest of the team cannot accomplish other mission objectives.

LxC score – priority weighted number in the cells of the 5x5 matrix, adopted from the ISS scorecard, which for each Risk, maps relevant combinations of likelihood and consequence scores assigned to a risk for a specific DRM and a particular Risk Impact Category. These scores are weighted based on scale definitions approved by the HSRB.

Medical - The care and treatment of an individual for illness or injury.

Mitigation Timeframe - the approximate timeframe when mitigations are expected to be completed.

Requirement – a documented physical or functional need originating from a standard.

Risk – is technically defined as the probability and magnitude of a loss, disaster, or undesirable event.

Risk Acceptance – a judgement made by the HSRB that countermeasures are effective and efficient for managing a risk, and no further risk reduction is considered worthwhile – e.g. when countermeasures are adequate, available, and will be included in future programs.

Risk-Based Decision-Making - Process that organizes information about the possibility of various outcomes occurring into an orderly structure that helps decision makes make better informed management choices.

Risk Characterization – the first category of deliverables in the Risk Mitigation Framework by which investments support effective risk reduction. Deliverables in this category contribute to an understanding of the magnitude of the impact of that risk on spaceflight crews and enable plans to decrease likelihood or consequence based on that understanding.

Risk Drivers - factors which describe how the spaceflight hazards, which are a feature of the spaceflight environment, have a material effect on each set of design reference mission attributes.

Risk Impact Categories - categories that identify domains of interest to NASA when Human Systems Risk is involved. There are currently three categories identified where risk consequence can impact either the crew or the agency. These categories are designed to illustrate the driving risk posture in each DRM category as appropriate.

1. **In-Mission Risk (Ops)** –the Risk Posture for crews in-mission defined by successful launch until successful and safe egress from the landing vehicle. The *Crew Health* impact subcategory identifies health issues while the *Mission Objectives* impact subcategory identifies crew performance decrements that can result in loss of mission objectives if realized.
2. **Flight Recertification** – applies when specific risk manifestation impacts the crewmember's physical or mental health after a mission, thereby delaying their flight certification and flight recertification. This applies throughout the career of an astronaut.
3. **Long Term Health (LTH)** – the lifetime impact of spaceflight on physical and mental health and performance of astronauts post flight including post-career. The LTH category consists of the *Health Outcomes* impact subcategory which includes medical conditions resulting from career exposures to the spaceflight environment, and the *Quality of Life* impact subcategory which identifies decrements in the ability of a post-flight astronaut to perform daily living activities as a result of career exposure to the spaceflight environment.

Risk Management – is defined as the identification, assessment, and prioritization of risks followed by coordinated and economical application of resources to minimize, monitor, and control the probability and/or impact of undesirable events.

Risk Metric – a measure to communicate progress on changes in Risk Posture based on evidence over time. It is based on available measures relevant to the consequence(s) that derives from evidence gathered from in-mission medical and research operations, spaceflight analogs, terrestrial analogs and animal models/data correlated with medical data from NASA databases (e.g. LSAH, LSDA), or environmental and terrestrial databases.

Risk Mitigation – the process of reducing a Risk's Likelihood or Consequence severity to the point of the Risk's acceptance or retirement. Risk mitigation activities and deliverables contribute to any of the following five categories: Risk Characterization, Prevention (Hazard Control), Consequence Reduction, System Resilience (Improve Margin), Risk Acceptance.

Risk Mitigation Plan – a plan implemented by Risk stakeholders that specifies deliverables, funding levels and schedule relevant to risk reduction. The merits of a set of risk mitigation plans are assessed by the HSRB using agreed upon Criteria and High Value Risk Mitigation Targets.

Risk-Neutral - Outcomes of programmatic decisions, proposed implementation, pursuit of standards/requirements deviations, and/or waivers do not change the overall likelihood and consequence to the health and human performance risk baselined by CHMO for a particular NASA program or project.

Risk Posture – The HSRB's understanding of a Human System Risk based on the assigned Risk LxC scores and Risk Dispositions for the purpose of communicating the agency's assessment of the state of the risk. This information is captured in a table contained in the Risk Summary slide shown in Figure D-12. Information directly supporting the Risk Posture is contained in the LxC Drivers and Risk Disposition Rationale sections.

(Risk) Retirement – a decision made by the HSRB to remove a Risk from regular reassessment by the HSRB when the consequences of that risk are determined to be of sufficiently low magnitude.

Subject Matter Expert - Person recognized as an expert in the technical area under review.

Standard – a document that establishes consistent methods, processes, and practices for health, medical, engineering or technical aspects of NASA programs. For example, there are health standards for crew selection and assignment, and technology standards for vehicle capabilities.

Technical Authority - TAs are part of NASA's system of checks and balances and provide independent oversight of programs and projects in support of safety and mission success through the selection of individuals at delegated levels of authority. TA delegations are formal and traceable to the Administrator. Individuals with TA are funded independently of a program or project.

Technical Standards - NASA documents that contain common and repeated use of rules, conditions, guidelines, or characteristics for products or related processes and production methods and related management system practices.

Uncertainty – the extent to which the true risk is not known and could include questions about causal pathways, measurement error, and sampling bias. Reported metrics should include some quantified measure of uncertainty (e.g. standard deviation, standard error, confidence interval, posterior distribution, credible interval).

APPENDIX B: ACRONYMS AND ABBREVIATIONS

Term	Description
AHRQ	Agency for Healthcare Research and Quality
CCP	Commercial Crew Program
CHMO	Chief Health and Medical Officer
CHS	Crew Health & Safety
CM	Configuration Management
CM	Countermeasure
CO2	Carbon Dioxide
CR	Change Request
CRM	Continuous Risk Management
DRM	Design Reference Mission
ECLSS	Environmental Control and Life Support System
EVA	Extravehicular Activity
gravity	1G
HEOMD	Human Exploration and Operations Mission Directorate
HH&P	Human Health & Performance Directorate
HHPCB	Human Health and Performance Control Board
HHPD	Human Health and Performance Directorate
HLS	Human Landing System
HMTA	Health and Medical Technical Authority
HQ	Headquarters (NASA)
HRP	Human Research Program
HSI	Human System Integration
HSRB	Human System Risk Board
ICP	Intracranial pressure
IMM	Integrated Medical Model
IOM	Institute of Medicine
ISS	International Space Station
JSC	Johnson Space Center
JSC CMO	Johnson Space Center Chief Medical Officer
L-	Launch minus (days)
L1/L2	Lagrangian point (mission destination)
LEO	Low Earth Orbit
LOC	Loss of Crew
LOE	Level of Evidence
LOM	Loss of Mission
LSAH	Lifetime Surveillance of Astronaut Health
LSDA	Life Sciences Data Archive
LTH	Long-Term Health
LxC	Likelihood versus Consequence
MD	Doctor of Medicine
MEDTED	Medical Technology Evaluation Demo
MORD	Medical Operations Requirements Document
MPCV	Multi-Purpose Crew Vehicle

Term	Description
MRI	Magnetic resonance imaging
MRL	Master Risk List
N/A	Not Applicable
NASA	National Aeronautics and Space Administration
NPD	NASA Policy Directive
NPR	NASA Procedural Requirements
OCHMO	Office of the Chief Health and Medical Officer
Ops	In Mission Operations
PRA	Probabilistic Risk Assessment
RIDM	Risk Informed Decision Making
RNFL	Retinal Nerve Fiber Layer
SBU	Sensitive But Unclassified
SCLT	System Capability Leadership Team
STD	Standard (NASA document)
TRL	Technology Readiness Level
TtO	Transition-to-Operations
TtP	Tests of Technologies and Procedures (

APPENDIX C: HUMAN SYSTEM RISKS MANAGED BY THE HSRB

Human System Risk	Short Title
Risk of Acute and Chronic Carbon Dioxide Exposure	*CO_2 Risk*
Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders	*BMed Risk*
Risk of Adverse Health & Performance Effects of Celestial Dust Exposure	*Dust Risk*
Risk of Adverse Health Effects Due to Host-Microorganism Interactions	*Microhost Risk*
Risk of Adverse Health Event Due To Altered Immune Response	*Immune Risk*
Risk of Adverse Health Outcomes & Decrements in Performance due to Inflight Medical Conditions	*Medical Conditions Risk*
Risk of Radiation Carcinogenesis	*Radiation Carcinogenesis Risk*
Risk of Adverse Outcome Due to Inadequate Human Systems Integration Architecture	*HSIA Risk*
Risk of Bone Fracture due to Spaceflight-induced Changes to Bone	*Bone Risk*
Risk of Cardiac Rhythm Problems	*Arrhythmia Risk*
Risk of Decompression Sickness	*DCS Risk*
Risk of Hearing Loss Related to Spaceflight	*Hearing Loss*
Risk of Impaired Control of Spacecraft/ Associated Systems and Decreased Mobility Due to Vestibular/ Sensorimotor Alterations Associated with Space Flight	*Sensorimotor*
Risk of Impaired Performance Due to Reduced Muscle Size, Strength & Endurance	*Muscle Risk*
Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight	*Pharm Risk*
Risk of Injury and Compromised Performance Due to EVA Operations	*EVA Risk*
Risk of Injury from Dynamic Loads	*Dynamic Loads Risk*
Risk of Injury from Non-Ionizing Radiation	*Non-Ionizing Risk*
Risk of Orthostatic Intolerance During Re-Exposure to Gravity	*OI Risk*
Risk of Performance and Behavioral Health Decrements Due to Inadequate Cooperation, Coordination, Communication, and Psychosocial Adaptation within a Team	*Team Risk*
Risk of Performance Decrement and Crew Illness Due to Inadequate Food and Nutrition	*Food-Nutrition Risk*
Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss , Circadian Desynchronization, and Work Overload	*Sleep Risk*
Risk of Reduced Crew Health and Performance Due to Hypoxia	*Hypoxia Risk*
Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity	*Aerobic Risk*
Risk of Renal Stone Formation	*Renal Stone Risk*
Risk of Spaceflight Associated Neuro-ocular Syndrome	*SANS Risk*
Risk of Toxic Exposure	*Toxic Exposure Risk*
Risk of Urinary Retention	*Urinary Retention Risk*
Risk to Crew Health Due Electrical Shock	*Electrical Shock Risk*
Concern of Venous Thromboembolism	*VTE*

APPENDIX D: BASIC RISK SUMMARY FIELDS

The HSRB Risk Management Office has developed standard PowerPoint templates that serve as bases for proposing or updating Risks or Concerns. The Risk Summary record within the template contains the primary information that describes the Risk.

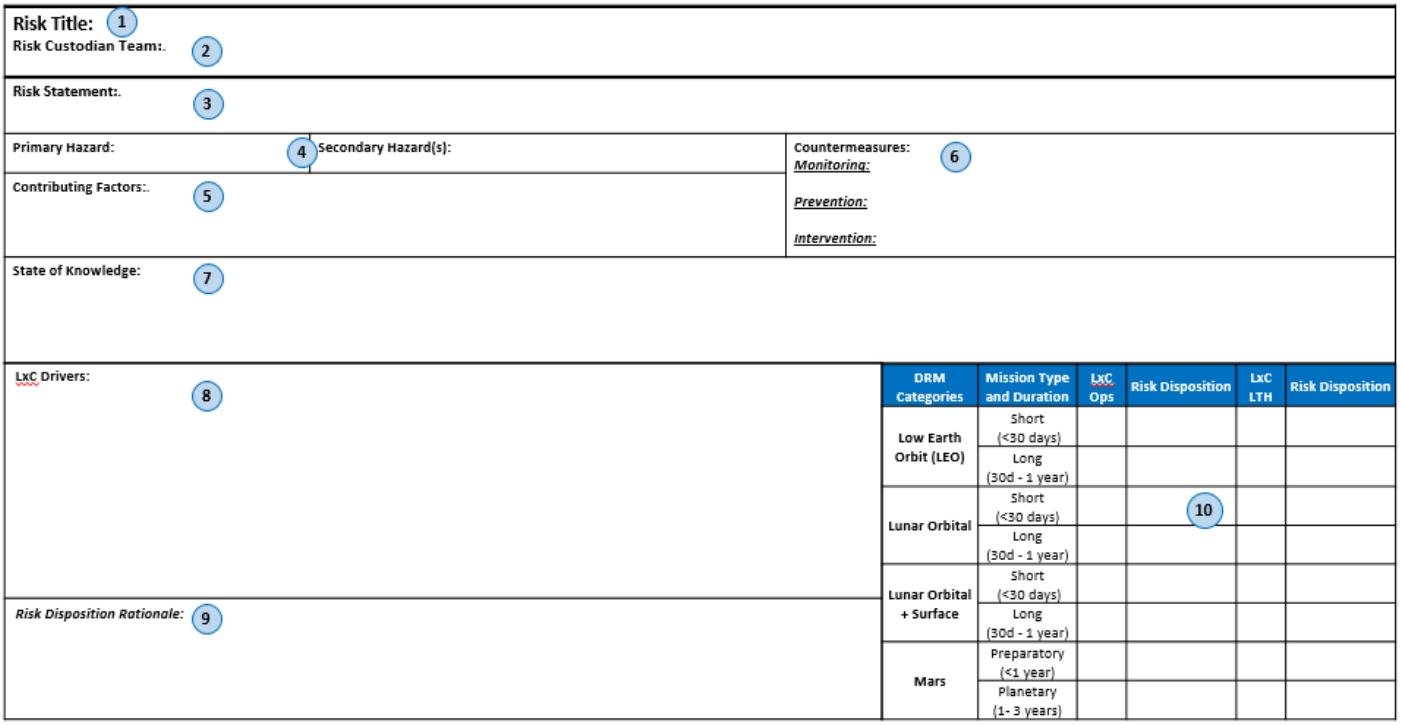

Figure D- 1: Risk Summary Template

The following items are descriptions of the fields in the Risk Summary record as well as standard content in the risk record template.

1. Risk Title

The Risk Title is a descriptive label that indicates the adverse outcome: "Risk of *'Outcome'*". A Risk Title can also be based on a factor influencing one or more human health or performance outcomes such as, "Risk of Adverse Health Effects and/or Performance Decrements Due to *'Inadequate Factor'*".

2. Risk Custodian Team

The Risk Custodian Team lists the three named Risk Custodians officially assigned to the Risk.

3. Risk Statement

The Risk Statement concisely describes a scenario relevant to human spaceflight missions that could potentially lead to negative outcomes that wholly or partially follow from the Risk at hand. Its general format is: "*Given that 'condition', there is a possibility that the 'negative consequence(s)' may occur".* The '*condition'* identifies changes in physiological or psycho-social metrics, or other factors attributable to one or more of the **Hazards** listed below, that in turn contribute to the Risk. For example:

"Given that exposure to a microgravity environment causes cardiovascular fitness (maximal aerobic capacity and submaximal performance capabilities) to decline, there is a possibility that mission task

performance would be impaired or tasks could not be performed."

In this example, the hazard is microgravity, the condition is a decline in cardiovascular fitness (specifically in the physiological metric of aerobic capacity) and the negative consequences are to the quality of mission task performance.

4. Hazards

Risks are derived from and grouped by common factors contributing to their potential occurrence. The HSRB uses a specific set of factors it calls hazards for this purpose. These hazards are:

1) Altered gravity
2) Radiation
3) Distance from earth
4) Isolation and Confinement
5) Hostile closed environment

The **primary hazard** as well as any applicable **secondary hazards** are identified for each Risk.

5. Contributing Factors

Contributing factors are items including any hazard or operational design and human system variable that influences the outcome(s) of concern for a Risk impacting human health and performance in spaceflight. It can be seen as a system variable whose state can contribute to mission success or failure and considered alterable through the implementation of risk mitigations.

6. Countermeasures

Countermeasures are actions, hardware/software or capabilities provided in-mission that serve to mitigate risk in the operational domain or in flight recertification or long term health for crews. These are intended to mitigate the risk and are classified into three types as they apply to Human System Risks:

- **Monitoring** – any actions, systems or capabilities implemented during the course of a mission used either operationally or for occupational surveillance to provide actionable information to crew or clinicians that can help (1) provide insight into prevention effectiveness and next step needs, or (2) provide insight into when to implement interventions associated with risk reduction. These apply to in-mission and in long-term health. Systems, sensors and data management needed for in-mission risk mitigation must be considered early in the design life cycle of the vehicle. Examples are: capability to sense and record vital signs; capability to determine crew time on exercise; capability to sense CO_2 in a suit; capability to sense radiation exposure throughout a mission; periodic medical exams to identify developing medical conditions.
- **Prevention** – any actions, systems or capabilities implemented pre-flight and during flight that decrease the influence of contributing factors and hazards on the risk or on the scenario that enables the risk to manifest. This also applies in the form of secondary prevention to minimize the likelihood of a small initial problem becoming a much larger and unmanageable problem for crews. Examples

are: exercise protocols to minimize bone and muscle loss; sleep aid medications to prevent sleep loss; noise reduction requirements and hearing protection to prevent hearing loss.

- **Intervention** – any actions, systems or capabilities applied after the risk scenario occurs intended to reduce the severity of the consequence. Examples are: special eye glasses to provide vision support; anti-emetic medications to decrease symptoms of space motion sickness; pain medication to reduce the impact of injuries on performance.

7. State of Knowledge

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.

8. LxC Drivers

The most dominant/impactful factor that 'drives' the LxC score is identified as an LxC driver. LxC drivers are identified for Ops, LTH and RTF (when appropriate) for given DRMs. Some drivers will apply to multiple DRMs. Applicable uncertainties and any additional factors that would support a risk-informed decision making process are included in this section. This information is consistent with the LxC assessment using the 5x5 risk matrix.

9. Risk Disposition Rationale

Relevant supporting context and assumptions behind the DRM Risk Dispositions are described in this section.

10. Risk Disposition and LxC Score per each DRM

This is a quick look at all of the L and C scores for the Risk as well as the Risk Dispositions delineated across the different DRMs as appropriate.

APPENDIX E: HMTA TRANSITION TO OPERATIONS (TtO) PROCESS OVERVIEW

The Transition to Operations review process is captured in NPR 8900.1B NASA Health and Medical Requirements for Human Space Exploration; Appendix D, Transition to Operations Review Process (TORP). That document describes the scope and applicability of the Transition to Operations (TtO) process, in addition to the OCHMO review, as the final step prior to implementation.

In practice, the TtO review process involves iterative actions and communication across several organizations including the Human Health and Performance Directorate (HH&P), the Health and Medical Technical Authority (HMTA), an implementing organization (often the Space Medicine Operations Division, but can be other SA Divisions), product supplier organizations (e.g., Human Research Program), and operational organizations (e.g., HMS system managers). Impacts across organizations and impacts to implementation should be carefully considered and communicated during TtO.

The development of the TtO decision package is the responsibility of the supplier organization, and the required content of the package is clearly stated in NPR 8900.1B. Supplier programs may use their own processes to document product development and impacts to human-system risks. The implementing organization is responsible for development of operational products, requirements, and associated training for spaceflight operations.

Agreements between the supplier organization, the implementing organization, and funding program(s) are made to document the responsibilities and expectations for the development and implementation of a deliverable. This interaction may result in changes to the scope, cost, or schedule. The main objective of this step is to document requirements, foster communication and ensure the appropriate deliverable/product is developed for implementation. The Space Medicine Operations Division Program Integration Office (PIO) can partner with these organizations to spotlight barriers and issues, resolve issues with implementation teams, provide traceability, and help engage the stakeholder community in the evaluation and decision-making process.

The HSRB serves as the body that reviews TtO decision packages and makes a recommendation to the JSC CMO. The board's responsibility is to weigh the evidence brought forth in support of the TtO candidate against the implementation plan and value to mitigating human-system risk. The outcome may be recommendation of a TtO candidate for approval by the CMO; to recommend approval of a TtO candidate with modifications to the CMO; or to not recommend a candidate to the CMO for approval.

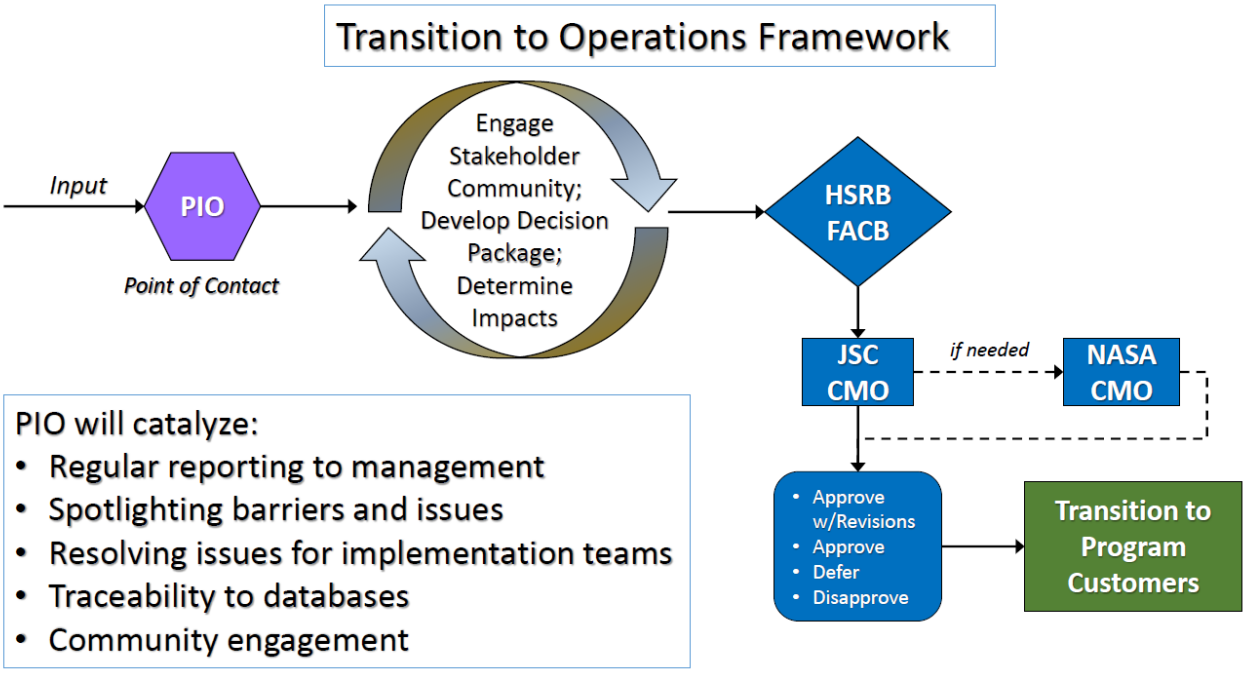

Figure E- 1: Process for Transition to Operations (TtO)

APPENDIX F: GUIDANCE FOR ASSIGNING LEVEL OF EVIDENCE

The Risk Custodian Team should start by referring to a set of causal criteria, derived from the A. Bradford-Hill Causal Guidelines. Of the original nine aspects of causal relationships against which evidence may be weighed, we use only six criteria. Table F-1 below shows these six criteria and provides a basic definition of each. The guidelines in Table F-1 are presented by order of necessity, and the progressive inclusion of more criteria is what informs higher Levels of Evidence.

Table F- 1: Sir A. Bradford Hill's causal guidelines employed by the HSRB for level of evidence assessment.

Criterion	Definition	Notes
Temporality	The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).	This is necessary for all posited causal effects, even speculative ones.
Analogy	The use of analogies or similarities between the observed association and any other associations.	Analogues can be in exposure, population, or both.
Mechanism	If there is a plausible theoretical mechanism that can explain how the causal effect works then the posited causal connection is more likely to be true.	
Reproducibility	Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an observed effect being causal.	
Specificity	Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.	This is the classic Person/Place/Time of epidemiology.
Coherence	Coherence between epidemiological and laboratory findings that validate the mechanistic assumptions increases the likelihood of an effect.	This is translational science.

The Level of Evidence score for each LxC score assigned to a DRM ranges from 1-4 and is based on the LxC Drivers presented in the risk package for each Impact Category (In-Mission, Return to Flight, Long Term Health) as described below:

Level 4: Speculative. This is the lowest level of evidence score and is reserved for causal effects that have little to no evidence to support them, but that may make theoretical sense given the current, limited sum of knowledge on a topic. In addition to *Temporality*, **Speculative** evidence will also have *Analogy*, either of exposure, population, or both, i.e. it will be a suggested relationship based on limited or incidental findings from ground-based analogues, occupational cohorts, or laboratory or animal studies. **Speculative** identifies areas where there may be uncertainty in risk assessment but that uncertainty does not drive changes in LxC assignment. It can identify potential areas for future research or occupational surveillance. In this case no evidence is available to support a linkage between the Hazards and claimed effects on humans that may lead to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority.

Example:

If the Risk Custodian Team for Behavioral Health focuses on ventricular changes in the brain that have been observed in astronauts after spaceflight as the LxC driver for a Mars mission DRM, then the Level of Evidence is *Speculative*. *Temporality* is addressed by Magnetic resonance imaging (MRI) findings before

and after spaceflight. *Analogy* is applied considering analogous terrestrial diseases associated with ventricular changes such as hydrocephalus. However the clinical definition of hydrocephalus is not met in the spaceflight cases, there are no identifiable clinical or operational impacts identified to date in the astronaut corps (not shown in the relevant population, therefore no *Reproducibility* or *Specificity)*, no measurements have been made in flight to support a proposed *Mechanism* of intracranial pressure (ICP) elevation, and some data in parabolic flights suggests the mechanism may be incorrect. In this example the proposed likelihood and consequence driving case for Long Term Health is **Speculative**.

Level 3: Weak. This category represents causal effects that are not well understood either epidemiologically or mechanistically. This level is differentiated from *Speculative* effects by the addition of a theoretical explanation of *Mechanism*. In practice, this means that the biological chain of events has been articulated but may not have been validated. Level of Evidence is stronger if the effect has been shown to be repeatable in other investigations. Note: *Mechanism, Reproducibility* or *Specificity* may be swapped, but Weak evidence generally only exhibits one of these three. *Weak* has limited impact on Risk assessment but may indicate the need for additional research to evaluate a concerning contribution to risk. *Weak* evidence may trigger a Concern. It indicates that the preponderance of available evidence suggests a possible linkage between the Hazard(s) and claimed effects on humans that may lead to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority.

Example:

If the In-Mission LxC Driver for human Behavioral Health impacts in a Mars DRM is considered to be space radiation, then the following example applies. Animal studies showing the effects of radiation on the brain establish *Temporality* because the effects are measured after radiation exposure. *Analogy* is established because brain regions are affected that reasonably contribute to behavioral outcomes measured in animals and may extend to humans. Studies have identified damage to the hippocampus in mice for example, possibly suggesting *Mechanism*. In some cases they may also approach *Reproducibility*, though when results are reproduced they are often with radiation types, doses and dose-rates that are not applicable to the exposures astronauts are expected to see in spaceflight and substantial reporting/publication bias of negative results may exist. *Specificity* in these cases is not met because of the lack of generalizability to human astronauts in addition to the lack of specificity with radiation type, doses and dose rates. The Level of Evidence assigned is **Weak** for the purposes of the Board. (Note: For animal studies to meet criteria for *Specificity*, the Risk Custodian Team must be able to demonstrate that the studies demonstrate attention to experimental design and external validation of translational research as shown in Table F-3 below.)

Level 2: Moderate. Causal effects in this category will have well-characterized epidemiological evidence to support them, though their biological mechanisms may not yet be fully validated. In addition to *Temporality*, *Analogy*, and *Mechanism*, ***Moderate*** evidence adds *Reproducibility* (reproduction of results by others) and *Specificity* in the evidence, i.e., the effect has been narrowed to a particular person/place/time that is generalizable to the astronaut cohort. For Animal or Cellular evidence to meet the *Specificity* guideline, the studies must demonstrate attention to experimental design and external validation of Animal Translational Research methods as discussed in Table F-3 below. ***Moderate*** evidence may trigger a Risk or justify advocating for design impacts or mitigation consideration in vehicle

requirements. It indicates that the preponderance of available evidence demonstrates a likely linkage between the Hazard(s) and claimed effects on humans that may lead to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority.

Example:

Spaceflight Neuro-Ocular Syndrome (SANS) has been observed in spaceflight and post-flight and is known to affect a significant number of astronauts. It has been a repeatable clinical finding, several mechanisms have been proposed (most notably increased intracranial pressure), and it is specific to astronaut crews. If the LxC driver for Long Term Health impacts in a Mars mission is based on clinical effects of elevated Intracranial Pressure, then this qualifies as **Moderate Evidence.** *Temporality*, *Analogy*, *Mechanism*, *Reproducibility*, and *Specificity* have been met to some extent, but *Coherence* is lacking. ICP increases have been measured post-flight in the astronaut population, but not in-flight. There is some evidence in parabolic flights suggesting ICP may not be elevated inflight. There are also no cases demonstrating clinical ICP effects outside of visual changes in existing Long Term health surveillance. The lack of *Coherence* among evidence sources that validate the proposed mechanistic assumption (i.e. that ICP increase leads to SANS) keeps this from being listed as **Strong** evidence for Long Term Health. The proposed outcome of Long Term health effects depends on the verification or disproof of that mechanism. Note: If the Risk Custodian Team limits their consequence to 'correctable visions changes', they could argue for a **Strong** Level of Evidence in both In-Mission and Long Term Health risks for most DRMs.

Level 1: Strong. This is the highest level of evidence, and represents causal effects that have attained broad consensus among subject matter experts. Connections that fit in this level will have high-quality epidemiological evidence in humans as well as laboratory studies describing mechanisms. In addition to having all the elements of the lower levels, **Strong** evidence will also have *Coherence*, which describes a correspondence between laboratory and human-subject results. Evidence that fits into the **Strong** category is of little doubt, and has been validated using multiple approaches. As such, the causal relationships that fit into this category are as certain as science may allow. **Strong** defines the ability to understand and effectively mitigate the risk. It indicates that the preponderance of available evidence demonstrates a strong linkage between the Hazard(s) and claimed effects on humans that rise to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority.

Example: The benefits of exercise as a general countermeasure for human health and performance issues in spaceflight meets the definition of **Strong** evidence. *Temporality* is met through early spaceflight missions showing deconditioning in the absence of exercise. *Analogy* is met through similar findings in bedrest analogs. *Mechanism* is generally understood in both terrestrial and spaceflight domains. Multiple studies on the ISS and other spaceflight examples have demonstrated the beneficial effects of exercise in slowing deconditioning among astronauts (*Reproducibility* and *Specificity*). *Coherence* is met through flights and studies across multiple domains including hindlimb unloading in rats, observed effects of bedrest on Earth, spaceflight observation and experiments that all validate both the mechanistic assumptions and demonstrate a clear likelihood of deconditioning if adequate exercise is not available to astronauts in flight. Therefore the Level of Evidence for stated LxC drivers for In-Mission Muscle Strength and Aerobic Capacity Risks can be considered **Strong**.

Table F- 2: A visual summary of the guidelines for causal criteria in each Level of Evidence assignment.

Specificity, Reproducibility, and Mechanism may each fill the requirement for an additional category to name

LOE	Temporality	Analogy	Mechanism	Reproducibility	Specificity	Coherence
4 - Speculative	✓	✓				
3 - Weak	✓	✓	✓			
2 - Moderate	✓	✓	✓	✓	✓	
1 - Strong	✓	✓	✓	✓	✓	✓

In providing guidance for assignment of Level of Evidence it is important to note that these are guidelines and not hard and fast rules. In some cases the role of Analogy, Specificity, or Reproducibility may be swapped to enable consideration of a higher level of evidence assignment. The Risk Custodian Teams are expected to use their professional judgement in making a recommendation to the Board.

Animal and Cellular Models

The categories of Animal and Cellular research can be particularly difficult to interpret in regards to human physiology and clinical concerns and so additional guidance is provided here. It is important for the Risk Custodian team to help board members understand the strength of evidence the animal or cellular model provides *when translating to human clinical or physiologic effects*. For the underlying pathophysiology on which the model is based, it is important to discuss the validity of the model, and the level of risk in using the model to make a prediction about human health and performance. In order to do that, some direction on how to determine if Animal or Cellular evidence can meet the criteria for *Specificity* of evidence as defined in Table F-2.

Animal and cellular/molecular research is initially assigned a **Weak** level of evidence. **Weak** has limited impact on Risk assessment but may indicate the need for additional research to evaluate a concerning contribution to risk. This is an initial default assignment that can be adjusted to a higher Level of Evidence if the Risk Custodian Team provides the board with a demonstration of how the study(-ies) address the criteria below to inform validity of translation to prediction for humans (*Specificity*).

Table F- 3: Studies eligible for a higher level of evidence demonstrate attention to experimental design and external validation of animal translational research methods, using animal models or cellular or molecular endpoints to generalize from animal to human.

	Considerations for Increasing Level of Evidence Recommendation for Animal/Cellular Studies
1.	Studies demonstrate relevant assessment and selection of animals (e.g., animal age relevant to human age translation; performance screening—higher performing animals selected similar to our astronauts; maintaining regimen of exercise and "fitness" levels).
2.	Studies demonstrate careful matching between experimental and control groups (e.g., sex, age, other characteristics).
3.	Evidence is provided for the appropriateness of animal strains for the question being asked (e.g., for almost all behavioral domains, researchers continue to use inbred isogenic strains such as C57BL/6 mouse strains but these can have both genetic and behavioral differences if coming from different breeders and that should be addressed).
4.	Blind-coding of all analyses (e.g., evidence coding of data by someone other than the researchers so that analysis can be performed in an unbiased manner) is performed and described in the methodology sections.
5.	Statistical approaches are rigorously conducted and adequately documented in methodology sections.
6.	Evidence of experimental results in independent cohorts at different times across different labs are present in the literature.
7.	Studies demonstrate use of multiple outcome measures, including measures that are functionally relevant to humans.
8.	Evidence that researchers have regularly tested their animal models for quality control (e.g., genetic drift, loss of phenotype) is shown and adequately documented in methodology sections.
9.	Evidence of validation across models and in the human condition are available in the supporting literature.
10.	Consideration and addressing of any negative data (e.g., false negatives/false positives) and study limitations are documented.
11.	Obligation to address any evidence or data that seems to contradict research being represented is considered in limitations sections.
12.	If a failure in translation has occurred, that should be addressed within the context of the following: Was it the animal model itself, the analysis, the clinical trial, or another factor?

Clinical Research Studies

The Evidence Based Practice Center supported by the Agency for Healthcare Research and Quality (AHRQ) provides guidance for grading the strength of evidence in the clinical domain. Grading of evidence requires assessment of specific domains including study limitations, directness, consistency, precision, and reporting bias. The definitions of these and approaches for evaluating evidence/studies in this manner is found at www.effectivehealthcare.ahrq.gov/reports/final.cfm. This provides supplemental guidance for assessing quality of evidence for clinical studies relevant to human spaceflight. Consideration of whether studies or reviews meet the definitions of *Reproducibility*, *Specificity*, and

Coherence should be guided by the quality of those studies as indicated in the AHRQ reference.

Further reading on assessing quality and strength of evidence can be found here:

1) Berkman ND, Lohr KN, Ansari M, McDonagh M, Balk E, Whitlock E, Reston J, Bass E, Butler M, Gartlehner G, Hartling L, Kane R, McPheeters M, Morgan L, Morton SC, Viswanathan M, Sista P, Chang S. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Comparative Effectiveness Reviews (Prepared by the RTI-UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No. 13(14)-EHC130-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

2) Institute of Medicine 2011. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13059.

3) Pound P, Ritskes-Hoitinga M. Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail. *J Transl Med*. 2018;16(1):304. Published 2018 Nov 7. doi:10.1186/s12967-018-1678-1

4) Ferreira GS, Veening-Griffioen DH, Boon WPC, Moors EHM, van Meer PJK. Levelling the Translational Gap for Animal to Human Efficacy Data. *Animals (Basel)*. 2020;10(7):E1199. Published 2020 Jul 15. doi:10.3390/ani10071199

5) Prabhakar S. Translational research challenges: finding the right animal models. *J Investig Med*. 2012;60(8):1141-1146. doi:10.2310/JIM.0b013e318271fb3b

6) Vandamme TF. Use of rodents as models of human diseases. *J Pharm Bioallied Sci*. 2014;6(1):2-9. doi:10.4103/0975-7406.124301

7) Smith AJ. Guidelines for planning and conducting high-quality research and testing on animals. *Lab Anim Res*. 2020;36:21. Published 2020 Jul 10. doi:10.1186/s42826-020-00054-0

8) Pound P, Ritskes-Hoitinga M. Can prospective systematic reviews of animal studies improve clinical translation?. *J Transl Med*. 2020;18(1):15. Published 2020 Jan 9. doi:10.1186/s12967-019-02205-x

9) Humer E, Probst T, Pieh C. Metabolomics in Psychiatric Disorders: What We Learn from Animal Models. *Metabolites*. 2020;10(2):72. Published 2020 Feb 17. doi:10.3390/metabo10020072

10) Donaldson ZR, Hen R. From psychiatric disorders to animal models: a bidirectional and dimensional approach. Biol Psychiatry. 2015;77(1):15-21. doi:10.1016/j.biopsych.2014.02.004

11) Aragona M. The Impact of Translational Neuroscience on Revisiting Psychiatric Diagnosis: State of the Art and Conceptual Analysis. Balkan Med J. 2017;34(6):487-492. doi:10.4274/balkanmedj.2017.1190

12) IOM (Institute of Medicine). 2013. Improving the utility and translation of animal models for nervous system disorders: Workshop summary. Washington, DC: The National Academies Press.

APPENDIX G: DIRECTED ACYCLIC GRAPHS

Risk Custodian Teams construct Directed Acyclic Graphs (DAGs) to illustrate the high-level story of how human exposure to the Hazards of spaceflight leads to meaningful mission-level health and performance outcomes. While DAGs are primarily used to inform the Health and Medical Technical Authority, they also are a tool for communication with HSRB stakeholders who are not likely to have deep expertise in the Human System domain, such as mission architects and program managers.

Introduction to DAGs and Causation

DAGs are a type of network diagram which, through specific conventions in their construction, represent causality in a visual format. Specifically, each directed arrow connecting one node to another on a DAG indicates a claim of causality. Causality is defined here to mean that the probability of realizing specific values of the random variable we identify as the effect varies over different values of the random variable that we claim are its causes. In simpler terms, we can imagine a binary factor that we suspect is causal: the probability of an outcome is different when the factor is present than when it is absent. Table G-1 shows an example of causal and non-causal relationships between two binary variables, A and B.

Table G- 1: Illustration of potential causal relationships between Factor A and Outcome B

	P(B=1 | A) when…	
Value of A	A not a cause of B	A causes B
0	0.6	0.6
1	0.6	0.8

As the first row in Table G-1 shows, when A is not a cause of B (A=0), the probability that outcome B occurs, P(B=1 | A), is 0.6 whether factor A is present or not. However, if A is a cause of B, then the probability of event B occurring is greater in the presence of factor A (0.8) than it is in absence of factor A (0.6).

A more concrete example could be the idea that ‘exposure to reduced gravity (i.e., less than 1G) causes a headward shift of bodily fluids’. In practice this means that the probability of observing a given amount of headward shift of bodily fluids is different depending on the gravity field to which astronauts are subjected.

Components of a DAG

Variables on a DAG are represented by circles, known as nodes (or sometimes vertices). Arrows in the DAG are called links (or sometimes edges) and represent causal relationships. Links are drawn starting at causes and terminating at effects.

Nodes that have one or more arrows coming out of them, with no arrows coming into them, are known as exogenous nodes. In DAGs for HSRB, exogenous nodes can be of several types: Spaceflight Hazards, Contributing Factors, and Countermeasures.

Spaceflight Hazards are the nodes that represent the unique characteristics of the spaceflight

environment which pose dangers to human health (either directly or through complex pathways). Since these are the ultimate source of danger, they are always exogenous.

Contributing Factors and Countermeasures represent factors that are exogenous, but are not Spaceflight Hazards. Exogenous, non-Hazard nodes that increase the probability that a Mission-Level Outcome will be experienced are Contributing Factors, while exogenous non-Hazard nodes that lower the probability that an outcome will be experienced are called Countermeasures. Heuristically, Countermeasures are typically factors that are introduced specifically to mitigate risk, while Contributing Factors tend to be the unintended consequences of circumstantial factors other than Spaceflight Hazards. Note that a particular node may simultaneously be a Countermeasure for one outcome and a Contributing Factor to another.

Nodes which have one or more arrows coming into them are called endogenous nodes. Endogenous nodes are of two types: Mission-Level Outcomes and Integral Factors. Integral Factors help complete the causal paths between Spaceflight Hazards and Mission-Level Outcomes and are essentially intermediate conditions on the path from exposure to outcome of interest.

Figure G-1 illustrates the various classes of nodes as described in 1-3 above:

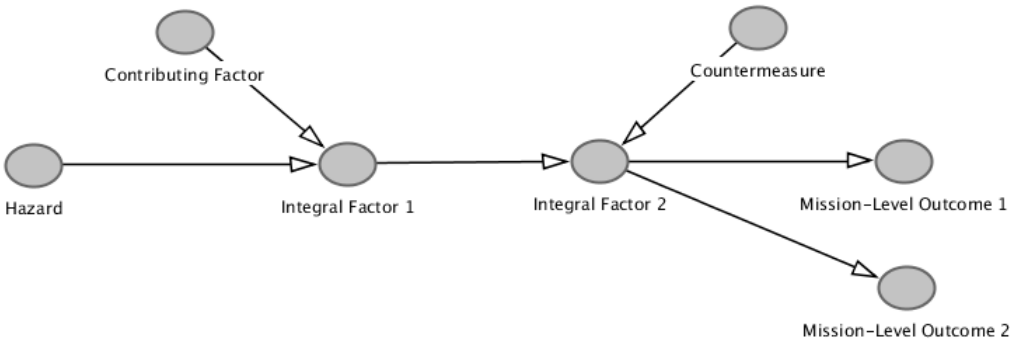

Figure G- 1: Example DAG which shows a Hazard, two Integral Factors, a Contributing Factor, a Countermeasure, and two Mission-Level Outcomes

There are additional labels we can use to describe the relationship between nodes, depending on their structural relationships/positions in the DAG. Note that these labels are always relative to a particular pair of nodes under consideration. Figure G-2 shows an example of these terms.

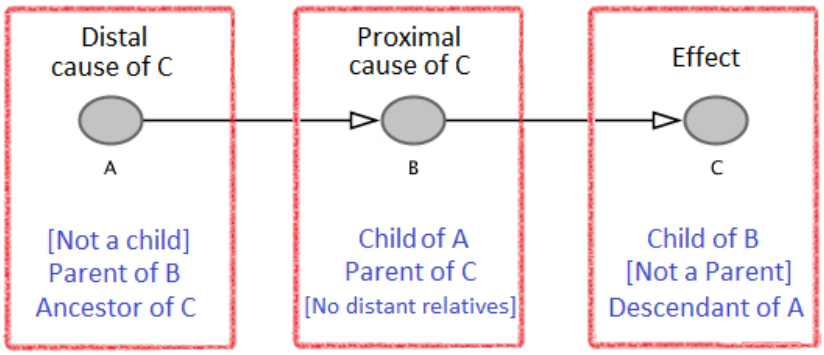

Figure G- 2: Example of casual relationship labels between a set of nodes

If a node has a direct causal connection to an outcome, it is a proximal cause. Alternatively, we can describe this in terms of familial relationships. Direct causes can also be referred to as parents to a particular effect. For example, in Figure G-2 node B is a proximal cause of node C. The direct connection from node B to node C also makes node B a parent of node C; in reciprocal fashion, node C is a child of node B.

If a node is instead further upstream from an effect of interest (i.e., does not have a direct connection to the outcome, but is still in a causal chain) we can refer to it as a distal cause. The familial term equivalent is an ancestor. Any effect that is downstream from a cause, but is not a direct effect is a descendant. In Figure G-2 we can see that node A is a distal cause of node C, or equivalently, node A is an ancestor of node C. This in turn makes node C a descendant of node A.

Instructions for DAG Creation

All DAGs should start with Spaceflight Hazards placed as nodes on the far left of the graph, and Mission-level Outcomes listed as nodes on the far right of the graph.

In keeping with the requirement that causes must precede effects, no feedback loops are permitted. In the case where the Risk Custodian Team feels a feedback loop is needed, the team must choose the most likely predecessor node and represent it earlier in the causal chain. It can be verbally explained during the risk presentation where feedback loops may exist without showing them on the diagram. However, it should be noted that, in reality, feedback loops are never simultaneous; they occur over a time span, even if that span is quite small. Therefore, if the team strongly desires to show feedback loops visually, DAGs can be drawn to reflect feedback loops as time-indexed variables causing each other over successive time frames.

When identifying nodes, the language used should identify a random variable rather than a realized value of a random variable. For example, a node should be named “Nutritional Status” (a random variable) rather than “Inadequate Nutrition” (a realized value of the random variable “Nutritional Status”). This provides maximum utility of the node in the DAG, as it reflects the idea that nutritional status may exert influence on various nodes when nutritional status is adequate or inadequate. This has the net effect of making nodes both risk-independent and DRM-independent. Part of the DAG process at a high level will be to reconcile terms with the common language used among all the DAGs, again to

guarantee risk- and DRM-independence.

To represent the known (or assumed) ties to other risks, placeholder nodes may be added to a DAG representing either incoming influence from another risk (other risks as contributing factors to the current risk), or outgoing influence to another risk (the current risk as a contributing factor to other risks). These ties should be represented as a single node with the name of the external risk and the arrows reflecting the direction of causal flow. Multiple arrows to this single node may be shown, but all must be the same direction. The nodes representing other risks should be simply named as the name of the risk, with "(Risk)" placed at the end of the name. To determine whether a risk should 'enter' or 'exit' from a particular DAG, reference Figure 10 (Risk Hierarchy) in the Risk Management Plan. Any risks that are more fundamental (lower on the pyramid) in this pyramid should be 'entering' the DAG and any risks that are more dependent (higher on the pyramid) should be shown exiting the DAG. If other risks are at the same level, then the Risk Custodian Team and choose to represent the connection in either direction.

Example: During the development of a DAG for an example Medical Risk, the team recognized that several unique factors in other risks contribute to the Medical DAG. Similarly, one of the unique integral factors in the Medical Risk DAG contributes to another individual Risk (Team). To represent these influences on the DAG, the RCT should add a node called "Team (Risk)" with an arrow pointing from one the DAGs nodes towards this external risk. Similarly, the RCT should add additional nodes representing other risks with arrows coming into the existing nodes on the Medical DAG.

Figure G-3 below shows an example Medical Risk DAG without Risk connections illustrated and Figure G-4 shows the same DAG with external Risks appropriately placed and connected. If multiple external Risks enter a single node, they can be grouped together and denoted as (Risks).

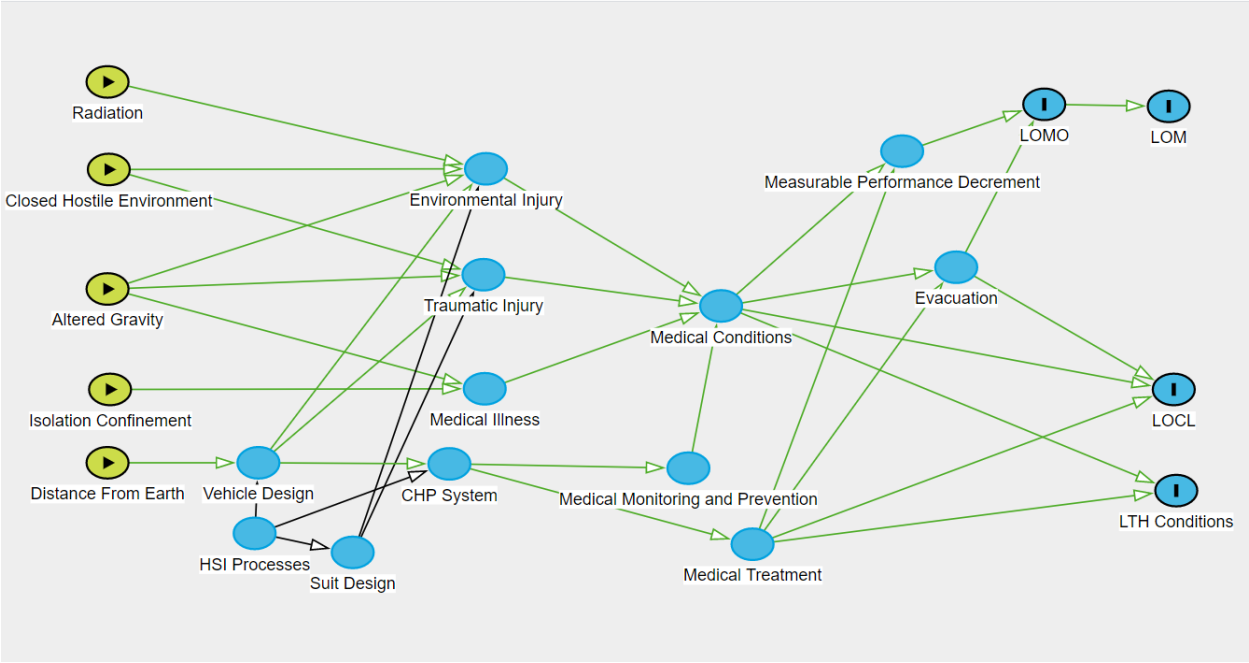

Figure G- 3: Example of DAG without connections to other Risks.

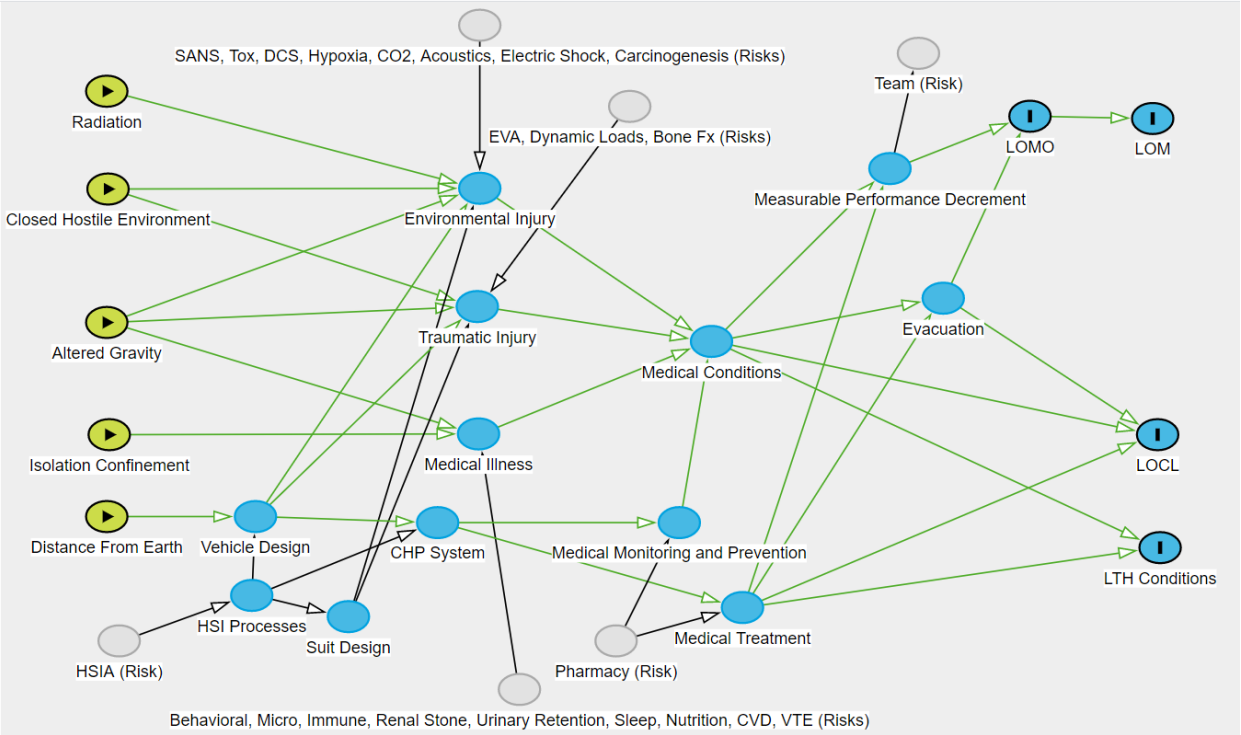

Figure G- 4: Example of a DAG with connections to other Risks.

Levels of Evidence in DAGs

For specific claims of causality on a DAG (i.e., for each arrow), a Level of Evidence (LOE) score is assigned using a set of causal criteria, derived from the A. Bradford-Hill Causal Guidelines. As in Appendix F, we use 6 of the 9 criteria posited and assign a level of evidence to each causal connection in the DAG. The definitions and scoring for evidence are similar to those used in Appendix F for assignment of Level of Evidence to LxC scores for a given DRM. The information is presented again here for completeness and the language is tailored to provide guidance for DAGs directly.

Table G-2 below shows these 6 criteria and provides a basic definition of each. The guidelines in Table G-2 are presented by order of necessity, and the progressive inclusion of more criteria is what informs higher levels of evidence. The LOE score is a link attribute, and will be captured as part of the information of the DAG. These scores will then be reflected in the visualization of the DAG.

Table G- 2: Sir A. Bradford Hill's causal guidelines employed by the HSRB for level of evidence assessment.

Criterion	Definition	Notes
Temporality	The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).	This is necessary for all posited causal effects, even speculative ones.
Analogy	The use of analogies or similarities between the observed association and any other associations.	Analogues can be in exposure, population, or both.
Mechanism	If there is a plausible theoretical mechanism that can explain how the causal effect works then the posited causal connection is more likely to be true.	
Reproducibility	Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an observed effect being causal.	
Specificity	Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.	This is the classic Person/Place/Time of epidemiology.
Coherence	Coherence between epidemiological and laboratory findings that validate the mechanistic assumptions increases the likelihood of an effect.	This is translational science.

The Level of Evidence score for each LxC score assigned to a DRM ranges from 1-4, as described below:

Level 4: Speculative. This is the lowest level of evidence score and is reserved for causal effects that have little to no evidence to support them, but that may make theoretical sense given the current, limited sum of knowledge on a topic. In addition to *Temporality*, **Speculative** evidence will also have *Analogy*, either of exposure, population, or both, i.e. it will be a suggested relationship based on limited or incidental findings from ground-based analogues, occupational cohorts, or laboratory or animal studies. In this case no evidence is available to support a linkage between the Hazards and claimed effects on humans that may lead to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority.

Applicability to DAGs: In DAGs, **Speculative** identifies causal connections that are intended to show hypothetical causal links that could result in elevated risk if they turn out to be true. These can identify potential areas for future research or occupational surveillance.

DAG Arrow Example: Ventricular changes in the brain have been observed in astronauts after spaceflight. Owing to the similarity of these changes to Hydrocephalus it has been suggested that these changes may cause clinical manifestations of this disease. However, beyond this analogy and the fact that the brain changes are observed post-flight, there is currently no evidence to support an arrow between Brain Ventricular Changes and Long Term Health outcomes. If this arrow is drawn on the DAG is should be labeled as **Speculative**.

Level 3: Weak. This category represents causal effects that are not well understood either epidemiologically or mechanistically. This level is differentiated from *Speculative* effects by the addition of a theoretical explanation of *Mechanism*. In practice, this means that the biological chain of events has been articulated but may not have been validated. Level of Evidence is stronger if the effect has been shown to be repeatable in other investigations. It indicates that the preponderance of available evidence

suggests a possible linkage between the Hazard(s) and claimed effects on humans that may lead to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority.

Applicability to DAGs: In the context of a DAG, **Weak** evidence indicates a domain where there is some limited evidence that the causal link exists, but it generally lacks two of the three options of *Mechanism, Reproducibility* or *Specificity*. **Weak** evidence identifies areas in the DAG where evidence clearly points towards a gap in knowledge that may warrant additional research to resolve.

DAG Arrow Example: Animal studies have demonstrated that ionizing radiation can affect cognitive functioning in mice. The studies generally meet *Temporality* and *Analogy*, but lack in *Specificity* and *Reproducibility*. If a Risk Custodian Team wishes to show the causal relationship between the Radiation hazard and cognitive function based on these studies alone, they would draw an arrow between Radiation and Cognitive Function nodes. This arrow should be labeled as **Weak** evidence.

Level 2: Moderate. Causal effects in this category will have well-characterized epidemiological evidence to support them, though their biological mechanisms may not yet be fully validated. In addition to *Temporality*, *Analogy*, and *Mechanism*, ***Moderate*** evidence adds *Reproducibility* (reproduction of results by others) and *Specificity* in the evidence, i.e., the effect has been narrowed to a particular person/place/time that is generalizable to the astronaut cohort. For Animal or Cellular evidence to meet the *Specificity* guideline, the studies must demonstrate attention to experimental design and external validation of Animal Translational Research methods as discussed in Table G-3 below. **Moderate** evidence may trigger a Risk or justify advocating for design impacts or mitigation consideration in vehicle requirements. It indicates that the preponderance of available evidence demonstrates a likely linkage between the Hazard(s) and claimed effects on humans that may lead to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority.

Applicability to DAGs: For a DAG, **Moderate** evidence shows that a causal connection likely exists and is likely to affect outcomes if not addressed. In addition to the criteria met by weak, this category includes evidence that can reasonably be construed to meet *Reproducibility* and *Specificity*. **Moderate** evidence shows areas where the evidence may support advocacy for inclusion of capabilities in mission.

DAG Arrow Example: In the case of SANS, an arrow drawn from Fluid Shifts to Intracranial Pressure Increase is labeled as Moderate Level of Evidence. Temporality, Reproducibility and Specificity are met as ICP elevations have been repeatedly measured in some post-flight crewmembers who also exhibit visual changes. Recent strict bedrest protocols on earth have been successful in reproducing some of the findings of SANS independent of spaceflight. The Mechanism of ICP elevation is proposed, but until in-flight measurements are performed there is not *Coherence* between post-flight measurements, parabolic flight measurements, and OCT data.

Level 1: Strong. This is the highest level of evidence, and represents causal effects that have attained broad consensus among subject matter experts. Connections that fit in this level will have high-quality epidemiological evidence in humans as well as laboratory studies describing mechanisms. In addition to having all the elements of the lower levels, **Strong** evidence will also have *Coherence*, which describes a correspondence between laboratory and human-subject results. Evidence that fits into the **Strong** category is of little doubt, and has been validated using multiple approaches. As such, the causal relationships that fit into this category are as certain as science may allow. **Strong** defines the ability to

understand and effectively mitigate the risk. It indicates that the preponderance of available evidence demonstrates a strong linkage between the Hazard(s) and claimed effects on humans that rise to clinically and operationally meaningful levels of concern to the Health and Medical Technical Authority.

Applicability to DAGs: For a DAG, **Strong** evidence shows that a causal connection exists and it will affect outcomes if not addressed. This level adds *Coherence* to the categories already met in **Moderate** evidence. Causal connections with **Strong** level of evidence may justify Health and Medical Technical Authority intervention with programs where risk mitigation is deemed insufficient for crews.

DAG Arrow Example: In the case of SANS, an arrow drawn from the structural change "Globe Flattening" to the functional change "Refractive Error Shift" is listed as **Strong** evidence. Similarly the line linking the countermeasure "Corrective Lenses" to "Refractive Error Shift" is listed as **Strong** evidence. In both of these cases there is a wealth of epidemiologic evidence, analog and laboratory studies that support the conclusion that changes in the shape of the eyeball result in vision changes and that glasses are able to correct the vision impact produced.

Table G- 3: A visual summary of the guidelines for causal criteria in each Level of Evidence assignment.
Specificity, Reproducibility, and Mechanism may each fill the requirement for an additional category to name

LOE	Temporality	Analogy	Mechanism	Reproducibilit y	Specificity	Coherence
4 - Speculative	✓	✓				
3 - Weak	✓	✓	✓			
2 - Moderate	✓	✓	✓	✓	✓	
1 - Strong	✓	✓	✓	✓	✓	✓

The simplest version of assigning a Level of Evidence includes differentiating only "Weak" vs. "Strong" evidence visually in a DAG (Figure G-5). This approach batches Level 3 and Level 4 evidence according to the definitions provided into a single 'Weak' category. Level 1 and Level 2 evidence is batched into a single 'Strong' category. Visually, the lines are differentiated on the DAG by assigning 'Weak' a dashed line and 'Strong' a solid line.

If more granularity is desired, each line in the DAG can be assigned a score of 1-4 according to the definitions in Table G-3. Table G-4 below shows how to record the structure of the DAG and the Levels of Evidence that accompany each connection therein. Figure G-5 is the visual representation of the data in Table G-3.

Table G- 4: Example data entry of a simple DAG, including LOE scores

Origin Node	Destination Node	LOE
A	B	3
B	C	2
B	D	4
C	E	1
D	E	3

Table G-4 records each connection in the DAG of Figure G-5 by putting the origin of the arrow in the "Origin Node" column, and the destination of the arrow in the "Destination Node" column. Each connection then receives its 1-4 LOE rating in the column marked "LOE". In Figure G-5 we can see a dashed line between node B and node D; the entry of "4" in the LOE column in the third row of Table G-8 reflects this as a *Speculative* connection. The causal arrow between node C and node E is thick, reflecting its LOE of "1" or *Strong*. The arrow connecting node A to node B is only slightly thicker than those connecting node B to node C and node D to node E, representing the LOE scores of "2", "3", and "3" respectively.

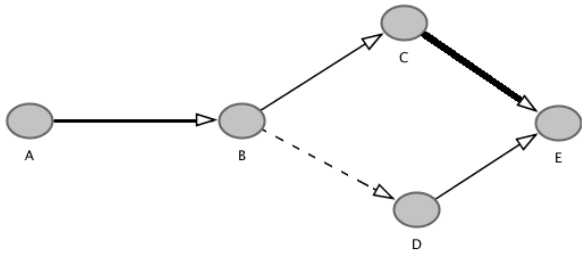

Figure G- 5: Example DAG showing LOE scores via different thicknesses and styles of arrows.

Each Risk Custodian Team will create a Levels of Evidence Table that includes an assignment of Level of Evidence for each of the connections between nodes that are represented in the final, configuration managed DAG for the risk. The team can choose between the Weak/Strong representation vs. the 1-4 scoring in conjunction with the Board Chair prior to presentation of the DAG at the Board.

Example Basic DAG and interpretation

Figure G-6 shows an example DAG that was generated for the SANS Risk; discussion follows.

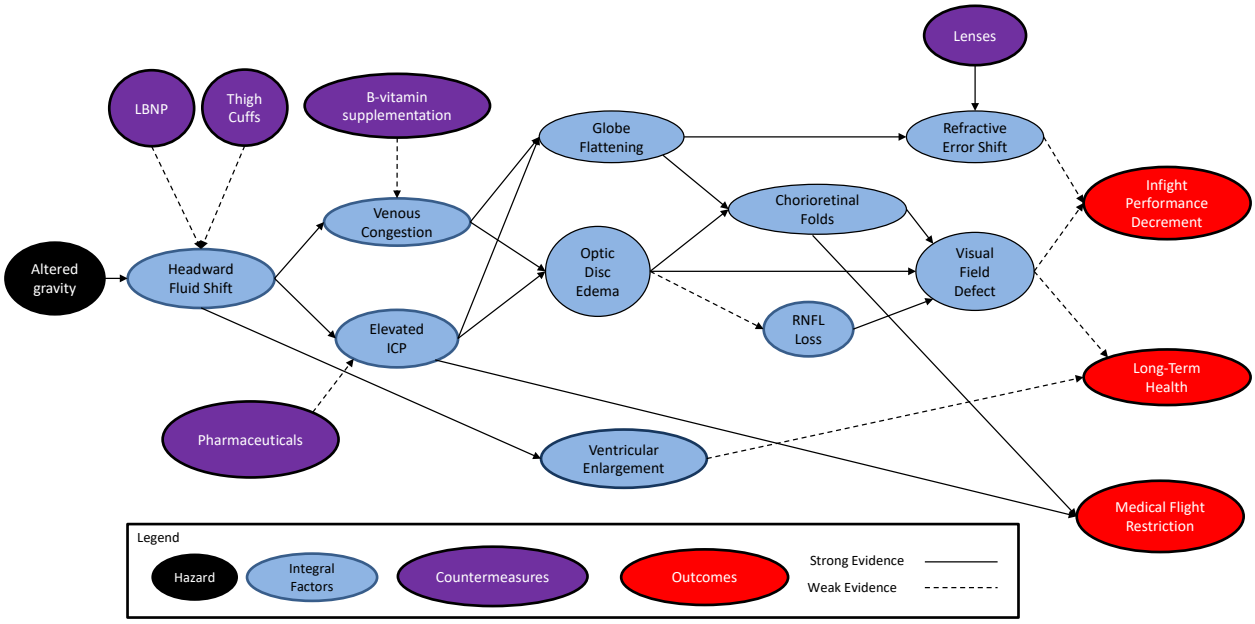

Figure G- 6: Example DAG for the SANS Risk.

This example includes differentiation by two Levels of Evidence (Strong vs. Weak)

In this example, one hazard is shown on the left side of the diagram: Altered Gravity. Following the causal chain forward from Altered Gravity, the subsequent node is Headward Fluid Shift which is a known consequence of weightlessness. That can lead to Venous Congestion and Elevated ICP. Elevated IPC has been measured post-flight in astronauts, but not in-flight. Either of these changes can lead to structural changes in the eye including Globe Flattening and Optic Disc Edema, both of which have been observed in astronauts in flight and post flight. These can cause Chorioretinal Folds which are also a structural change to the eye observed in spaceflight. There is **Weak** evidence to support the concern that Retinal Nerve Fiber Layer (RNFL) Loss is a potential consequence of Optic Disc Edema. *Temporality* and *Analogy* are satisfied by terrestrial disease analogs, but *Specificity* is not met in the Astronaut Corps and *Mechanism* is in question due to uncertainties surrounding the cause of Optic Disc Edema. Because of this the arrow connecting Optic Disc Edema to RNFL Loss is visualized by a dotted line. Similarly other Integral Factor Node connections throughout the causal chain are illustrated by solid (**Strong** evidence) or dotted (**Weak** evidence) lines to the corresponding effects.

Countermeasures here are shown as purple external nodes that connect to the Integral Factor Nodes that they either prevent or treat. Lenses have been used extensively in spaceflight to correct the vision impairment caused by the structural changes observed in SANS and the connection between Lenses and Refractive Error Shift is shown as a solid (**Strong** evidence) line. Similarly, Pharmaceuticals are proposed as a possible countermeasure to lower Intracranial Pressure (ICP), but have not been used for this specific condition and have not been used in spaceflight. From that perspective they do not meet *Specificity* or *Reproducibility*. Therefore, the line connecting Pharmaceuticals to Elevated ICP is dotted (**Weak** Evidence or in this case a Potential Countermeasure).