The Human Research Program for Civilians in Spaceflight and Space Habitation (HRP-C)

Editors

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Acknowledgement

The HRP-C Planning Committee recognizes the extraordinary contribution of government space agencies to the human exploration of space and human exploration in general. They have given civilization what it knows about human spaceflight today. Without these efforts, there would be no human exploration of space.

EXECUTIVE SUMMARY

Background

Commercial spaceflight is fast becoming a vibrant and robust sector of the global economy. As this economy further expands, the number of civilian tourists and the civilian workforce will expand with it. Although we know a great deal about the health and performance effects of spaceflight on professional astronauts, the civilian population is composed of quite a different demographic. Greater than fifty percent of the United States (U.S.) population has one or more chronic health conditions, such as arthritis, diabetes, atrial fibrillation, high blood pressure, asthma, migraine headaches, and kidney disease. Further, approximately two out of three Americans experience some level of cognitive impairment as they age and one out of five individuals have disabilities, such as cerebral palsy, spina bifida, spinal cord injury, multiple sclerosis, Parkinson's disease, hearing loss, visual disorders, brain injury, autism, and mental health disorders. As civilians with health and behavior challenges venture into space, we need to understand how spaceflight stressors, such as microgravity, radiation, isolation, confinement, and distance from Earth, impact these civilian comorbidities and develop effective countermeasures so that they may safely travel, live, work, and thrive in space.

Objectives

The proposed Human Research Program for Civilians in Spaceflight and Space Habitation (HRP-C) is based upon 6 main objectives. (1) To identify high priority research so that data collection can begin now and continue as the number of civilian travelers increases; (2) To provide harmonized data collection strategies that will benefit all stakeholders; (3) To accelerate biomedical discovery through comprehensive metrics; (4) To complement the extant literature on professional astronauts with data from the diverse civilian population; (5) To include a foundational capability to seamlessly guide the research; and (6) To develop effective countermeasures to the space hazards, allowing spacefaring civilians to travel in safety and in good health.

Methodology

To develop this comprehensive research program, a committee was formed of spaceflight experts, scientists, spaceflight providers, medical experts, and space agency representatives. Regular think-tank sessions were held over an 8-month period. A summary of this committee's advice is provided in this report.

Results

The result of these efforts is a foundational and comprehensive Human Research Program for Civilians in Spaceflight and Space habitation (HRP-C) aimed at gathering and analyzing health and performance data, and developing countermeasures for those who fly into space. The Program is organized into 3 Tracks.

Track 1 research recommends a comprehensive and (commonly) untargeted set of health and performance measures across design reference missions to more deeply describe the spaceflight response, identify novel countermeasure targets, and develop new hypotheses for future research. Casting a wide net of measures should speed discovery in the civilian population through analysis of these high dimensional data sets by identifying patterns of variance (change) across all missions, regardless of mission parameters or flight provider. The approach also enables the ability to compare missions across countries, as other countries adopt this harmonized methods approach. Track 1 research will also provide insight into preventive and therapeutic strategies to reduce risk impact, as the focus is development of reliable countermeasures.

Track 2 applies focused, hypothesis-driven research based on known spaceflight risks and on new risks that may be elucidated in the future. Similar to the NASA HRP, each risk will require the evaluation and funding of individual research proposals based on the urgency and consequences of the problem being studied (as well as the merits of the proposal). The research will require validated, reliable, and sensitive measures and established experimental controls.

Track 3 refers to the overarching organizations (or offices) that direct the research performed in Tracks 1 and 2. These organizations include such things as a board that prioritizes and oversees the research, a board that ensures the ethical treatment of the civilian space force in the conduct of the research, designated entities that control research data maintenance (both bio and behavioral), an independent, non-regulatory system for the collection of space health reports made by the primary stakeholders (i.e., civilian space travelers, spaceflight providers, private sector enterprises, the scientific and medical research community, and government and private funding enterprises), and others. Designated organizations will also ensure continued, integrated, and cross-cutting attention to training, countermeasures development, procedure development, and other critical capabilities.

Conclusion

The data collected, analyzed, and reported under the HRP-C will enable the growth of a robust civilian spacefaring community. As duration and distance of commercial space missions grows, the medical implications and the need for greater expeditionary fitness, self-awareness, and preventive measures grows with them. A health research and monitoring program with adequate numbers of participants is needed to advance the new space industries into a thriving present, and a robust future. Fundamentally, this HRP-C initiative will itself thrive when the active participation of those actively involved in taking civilians into space become engaged with one another in true collaboration.

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“Our mission is to do our best

to make it possible for everyone who wishes to

enter space to realize that dream through advanced science.”

ABSTRACT

The Human Research Program for Civilians in Spaceflight and Space Habitation (HRP-C) is the foundational program to address the health, safety, and performance of civilian space travelers in the commercial space sector. Various government organizations such as CSA, NASA, JAXA, ESA, and others have foundational human research programs addressing the needs of professional astronauts engaged in exploration missions. However, to date, there has been no dedicated effort with sufficient scope to address the widespread needs of civilian space travelers. The HRP-C has been established to fill this gap. In creating the first comprehensive foundational human research program for civilians, the HRP-C recognizes the numerous organizations and programs that currently address specific forms of human research within the civilian space medicine community. The HRP-C effort welcomes collaborations with these groups. Where HRP-C differs is in the comprehensive spectrum of needs that are addressed for civilian space travelers of all nations and for the space industry as a whole. While the HRP-C has been established with U.S. roots, it has incorporated international collaborators who have expressed an interest in taking the model of the HRP-C into their respective nations. This presents the opportunity for harmonization of methods across national programs and the ability to more easily compare findings, which is expected to more rapidly accelerate and scale advances in the field to the benefit of the worldwide commercial spacefaring community.

1.0 INTRODUCTION

Until recently, individuals who traveled in space have predominantly been professional astronauts. As a population of space explorers, they were physically fit, uniquely educated, trained for years in preparation for space travel, and willing to take risks that may lead to serious injury or death.

At the summer 2020 meeting of the National Space Council (NSpC), the need to make space accessible and safe for average civilians traveling in commercial space vehicles was proposed. Interest in this goal was prompted by developments in the commercialization of space by the space industry and governments who perceived a future, booming space economy. Advances in protecting career astronauts from space hazards led to the conclusion that strategies to mitigate the adverse health effects of microgravity and space radiation on this unique population could be readily used to protect the population of average civilians, many with chronic health conditions and disabilities. However, a scientific literature review of NASA-funded human health research indicated that there remained many unanswered questions about space hazards and effective countermeasures, such as the effects of variable gravity and space radiation (Goldhagen, 2015; Marge, 2021; Sobel & Forsley, 2023).

In response to the 2020 NSpC's recommendation about making space accessible and safe for average civilians, Dr. Michael Marge, serving in the Office of the Secretary of the U.S. Department of Health and Human Services, submitted a proposal to develop the first ever human research program for civilians in spaceflight and space habitation. The NSpC tacitly approved the proposal and referred it to the Commercial Spaceflight Federation (CSF) for support and implementation. Beginning in October 2020, an HRP for Civilians in Commercial Space Workshop Planning Committee was created. The Committee was composed of 35 experts from all sectors of space research who worked together for eight months to develop the initial HRP. The Planning Committee was divided into two subcommittees. The subcommittee on Suborbital Spaceflight was chaired by Dr. Mark Shelhamer of Johns Hopkins University School of Medicine. The subcommittee on Orbital and Beyond Low Earth Orbit Spaceflight and Habitation was chaired by Dr. Michael A. Schmidt, CEO and Chief Scientific Officer of Sovaris Aerospace.

The draft HRP document was the focus of a May 11-12, 2021, CSF Workshop with more than 100 stakeholders providing further input and recommendations to refine the HRP. Following the Workshop, the HRP for civilians in space was submitted to the United States Administration and to the Congress for support and implementation. Although interest in implementation was high, it was recommended that the HRP become more comprehensive in scope, benefit from new information about human health in space, and become a model that can be applied globally.

In March 2023, Dr. Marge approached Dr. Bettina L Beard of the NASA Human-Systems Integration Division and Technical Chair of the International Association for the Advancement of Space Safety (IAASS) Human Performance & Health Technical Committee (HPH TC) to chair the HRP Advisory Group. A proposal to revise, update and broaden the original HRP was submitted by Drs. Beard and Marge to the IAASS Executive Committee. IAASS approved to support the project in April 2023.

Since that time, a group of 32 national and international experts in human space research called the IAASS Workshop Planning Committee* have worked together bi-weekly to develop a revised HRP for Civilians that includes a plan of action that:

(1) describes a comprehensive human research program

(2) broadens the scope of the initial bio-medically based HRP by expanding the behavioral health component and putting greater emphasis on the task performance of average civilians in space travel, habitation, and work

(3) facilitates and encourages international cooperation and data sharing

To accomplish these goals, three subcommittees were created: Subcommittee on Human Health and Performance (HHP) chaired by Dr. Michael A Schmidt, CEO of Sovaris Aerospace, to describe the full spectrum of human health and performance research needs focused on reducing risks from space hazards, advancing protection of human health, and supporting optimum performance of average civilians in space (see Sections 2-5); Subcommittee on Design Reference Mission (DRM) chaired by Dr. Angie Bukley of The Aerospace Corporation, whose goal was to identify the space environment challenges for different mission profiles ranging from sub-orbital to interplanetary flights (see Section 6.0); and the Subcommittee on Implementation chaired by Dr. George Nield, Chair of the Global Spaceport Alliance, whose mission is to recommend strategies that will result in the funding and administration of the revised HRP (to be discussed in a separate report).

The need for an HRP for civilians in space has become more urgent as a result of the current US government administration's initiative to "prepare for the future space workforce." On September 9, 2022, Vice President Harris, Chair of the National Space Council, announced this need at a meeting of the NSpC. She envisioned that space will be commercialized in the coming decades and will develop a robust job market available to average civilians. As such, it will be important to ensure safe and healthy working conditions for civilians in space through effective research, education, and training. Although NASA is focused on space exploration, it supports the commercialization of space and is providing support for the development of three commercial orbital platforms which will be launched in the next decade. The space companies that will build

and operate these orbital platforms will require expertise from a broad range of professions and technical specialties. In addition, we anticipate commercial stations in orbit around the Moon, on the surface of the Moon and asteroids.

In the pages that follow, the recommendations of the IAASS Workshop Planning Committee are presented, representing a comprehensive human research program for civilians that the Committee has determined are foundational to optimizing the health, safety, and performance of average civilians who will be populating space in the thousands as tourists, habitants, and workers in the coming decades. The proposed recommendations will benefit all stakeholders in the commercialization of space—governments, the space industry, and most importantly, the civilian who chooses to travel, live, or work in future space.

1.1 HRP-C LEADERSHIP & COMMITTEE MEMBERS

Planning Committee Leadership

Bettina L Beard, PhD (NASA) Chair, Michael Marge, EdD (SUNY Upstate Medical University), Vice Chair and Co-Editor of this Report.

Human Health and Performance Committee: Michael A. Schmidt, PhD (Sovaris Aerospace), Chair

DRM Committee: Angie Bukley, PhD (The Aerospace Corporation), Co-Chair; Sarah E. Georgin, PhD (The Aerospace Corporation), Co-Chair

Implementation Committee: George Nield, PhD (Global Spaceport Alliance), Chair

**Planning Committee Members*

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Exploration Agency); Seamus Thierry, MD (South Brittany General Hospital, France); Sheri Wells-Jensen, PhD (AstroAccess); H. R. Zucker (AstroAccess).

1.2 COLLABORATIVE FOUNDATION

At the core of the HRP-C is collaboration. Collaboration exists when each of the involved parties have their fundamental needs met. While there are many parties that will interact with the HRP-C, there are four primary stakeholders whose needs are held as central to a thriving research effort that will lead to the successful expansion of commercial spaceflight. These are:

1. Civilian space travelers
2. Spaceflight providers and private sector enterprises
3. Scientific and medical research community
4. Government and private funding enterprises

The HRP-C was established with contributions from individuals who reflect the interests and expertise of each of these four groups. This Report is intended to serve as the foundational architecture that guides the thoughtful establishment of the overarching HRP-C program. While each element of the human research program is described in concept below, its full implementation will only occur when the organizing foundation and funding are in place. From there, the refined operational details of the HRP-C will be formally constructed and will be accomplished in a collaborative fashion between the stakeholder groups.

In practice, we intend that the collective vision of each of these four interest groups will converge to form that which could never be formed by any one group alone. Such a collaborative vision, while not without challenges, is expected to accelerate our emergence in this next wave of becoming a space faring civilization. As such, the depth of our commitment to this collaboration has the ability to shape the next 50 years of humans traveling, living, working, and thriving in space.

In concert, the HRP-C initiative recognizes the extraordinary contribution of government space agencies to the human exploration of space and human exploration in general. They have given civilization what it knows about human spaceflight today. This includes NASA, Roscosmos, ESA, JAXA, and others. Without these efforts, there would be no human exploration of space.

In the development of the current HRP-C, physicians, scientists, and engineers (active and retired) from NASA, JAXA, ESA, and other agencies have served as active members of the HRP-C committees and have contributed significantly to its development. This includes attention to maintaining best practices in alignment with the successful human exploration of space to date. With that said, opinions presented in the HRP-C document herein are the sole opinions of

the individual committee members and do not represent the official position of NASA or any other space agency.

At its core, the HRP-C is a biomedical research program. As such, it is useful to offer a distinction between human research and clinical medicine. The HRP-C recognizes that the responsibility to determine who is cleared to fly into space rests with the individual space traveler, his or her health care provider, and the flight providers. It is a medical decision that is wholly outside the purview of the HRP-C.

Therefore, the mission of the HRP-C is to conduct as extensive a form of human research as is permissible on those who 1) elect to fly into space, 2) have received clearance from their physician and the flight provider, and 3) have given their fully informed consent. A foundation of the HRP-C mission is to gather and analyze data in those who do fly into space under the dictum, "first, do no harm." A primary aim is that this research enables more robust informed consent in the future for those who wish to fly into space and that the derived countermeasures can be optimized for all who fly in space. It is the research of the HRP-C over time that will provide continuing insights that will help guide the advice of physicians and flight providers *who bear the official responsibility* of determining (along with the passenger) who will fly into space.

As such, the HRP-C is seen as being in full collaboration with the space travelers, their clinicians, and the flight providers in collectively better understanding how to optimize the spacefaring experience.

1.3 NON-REGULATORY

The HRP-C is designed as a comprehensive research program that serves the interest of optimizing the human's ability to live and thrive in space. It is expected that the data and knowledge generated from this effort will serve the interest of any group interested in advancing human spaceflight. At its foundation, the HRP-C has no regulatory function and no ability to promulgate rules of any kind that would govern the commercial space industry. That function is the responsibility of other bodies.

1.4 UNIQUE CHARACTERISTICS OF THE CIVILIAN SPACE TRAVELING COHORT

Commercial spaceflight is fast becoming a vibrant and robust sector of the global economy. As this economy further expands, its civilian workforce will expand with it. Indeed, commercial spaceflight is poised to field one of the most advanced and technical labor forces in modern times. The recruitment, training, and maintenance of this workforce will be of great importance to industry and governments that recognize their role both for building and growing the commercial sector and building the national economies. Maintaining the health, safety, and

performance of space travelers will differ from the manner in which NASA, ESA, JAXA, and other organizations address the needs of professional astronauts engaged in exploration missions. The differences will occur, first, because of the vast number of people who will now be traveling or working in low earth orbit or on the Moon. Second, there will be differing groups that will be using spaceflight, namely tourists, flight crews, industrial workers, and scientists.

For instance, the International Space Station (ISS) was first crewed on November 2, 2000. In the 23 years of continuous ISS habitation, there have only been 142 individual crew members (astronauts or cosmonauts) who participated in missions lasting weeks to months. Some crew members have had 2 to 5 ISS missions during their careers. Currently at NASA there are only 39 flight assignable astronauts who are inflight, recently returned from a mission, or now assigned to upcoming missions. NASA career astronauts are selected for meeting exacting medical standards and must continually maintain fitness for duty. Their health and performance are closely monitored and any changes in their health must either be “fixed” or the risk to the astronaut or for the success of the mission must be deemed acceptable.

The small cohort of NASA astronauts are initially highly screened, go through 2 years of training to become an astronaut and, when assigned to a flight, may spend 1-3 years on specific training for that space mission. Importantly, professionally trained astronauts have dedicated programs to maintain their fitness, as well as dedicated medical teams that provide advanced medical care focused specifically on thriving in space.

The astronaut hiring and training scenario is not compatible with a vigorous, fast moving, innovative civilian spaceflight industry. The number of civilian spaceflight participants is anticipated to quickly dwarf the NASA effort. These will include tourists who seek the experience of microgravity and a tour of the Moon (infrequent space travelers); spaceflight crew who will operate space vehicles (regularly scheduled flights to and from space); industry workers who will run the food service, accommodations, habitat maintenance, etc.; and specialized workers who work at the new commercial industries that can successful use either microgravity in LEO for manufacturing or resources on the Moon for the betterment of terrestrial life (live and work in microgravity or on the Moon for extended durations). The above is noteworthy when considering the limited data available for determining potential civilian health risks associated with spaceflight or living in partial gravity, e.g., the Moon.

The large civilian space traveler pool will extend across a continuum of phenotypes representing various states of health. In many ways, the civilian space traveling cohort is not unlike the cohort that embarks on adventure travel and remote wilderness expeditions. This cohort involves the extremely fit and well trained, such as those who might summit Mount Everest. These commonly exceed astronauts in fitness. But spaceflight is also expected to involve those who are untrained,

overweight, deconditioned, possess several comorbidities, are nutritionally deficient, possess variable disabilities, and use multiple medications. Notably, the CDC reports that 51% of the U.S. population have one or more chronic health conditions and one in five have a disability.

Though astronauts do develop comorbidities as they age (and whereby spaceflight itself is an accelerated aging paradigm), these conditions are 'stabilized' before going back into space. In addition, the number of astronauts and thus the number of comorbidities flown in space to date is small. In accordance, the associated spectrum of comorbidities studied in space is small. It is expected that the breadth of comorbidities presented by the civilian population will quickly exceed that presented by the professional astronaut corps. This is something for which we have limited data and urges a comprehensive research effort.

In the near future, commercial missions will extend beyond 30 days. When commercial lunar flights emerge, the duration may be short, but the radiation exposure will be greater. As duration and distance of commercial space missions grows, the medical implications and the need for greater expeditionary fitness, self-awareness, and preventive measures grows with them. A health research and monitoring program with adequate numbers of participants is needed to advance these new space industries into a thriving present and a robust future.

1.5 CONTINUUM OF MISSIONS AND PRIORITY SETTING

It is useful to understand three features of the HRP-C scope, as one contemplates how to best use HRP-C resources. These features are spatial, temporal, and functional.

Encompassed within the spatial domain is the variability in mission parameters (characterized by the DRM; design reference mission). Commercial space flights will enter suborbital, orbital, lunar, and space beyond. Each will possess its own mission parameters, as described in more detail in Section 5.0.

The second is the temporal domain, referring (in this case) not to mission duration but to the length of time it may take before commercial passengers and crew realistically embark on such missions. For example, if we do not intend to land civilians on the Moon before ten years, how should we prioritize research for this spatial domain?

Third is a functional domain, meaning what is the function and purpose of the mission? Tourism, scientific research, manufacturing for usage on Earth, manufacturing for use in space, mining, construction of structures in space, and others are among these. If we are progressing rapidly toward workers in space, then there is a more pressing need to address occupational health. If it is initially mainly tourists, then the focus on occupational health concerns may be delayed. Either way, it is justifiable that the HRP-C establishes timelines for each.

Considerations such as these will be among the driving forces in how research priorities are set. And these forces themselves are driven by commercial dynamics that are outside the control of the HRP-C. Nevertheless, the HRP-C must be attentive to them and adaptable in constructing a research platform that is nimble and responsive to such market forces. The beauty of the HRP-C as currently conceived is that it is quite ready to address these needs regardless of which direction the market forces take it, while continuing to adhere to sound research principles.

1.6 HEALTH, SAFETY, AND PERFORMANCE

While all missions into space carry a known set of inherent biomedical risks that are important to identify, it is also important to focus the effort of the HRP-C on the means by which we can support the thriving of individuals, teams, and communities in space. Thriving is a condition beyond mere survival, implying a condition where one is able to remain healthy, flourish and prosper. It encompasses the ability to not only meet the demands of specific mission parameters but to do so with resilience and return to Earth in as optimal a state as possible.

Fundamental to this objective is the optimization of health, safety, and performance. As an operational precept, health can be defined as the innate ability to avoid injury and illness under stress. Safety refers to the process of creating an environment that minimizes the risk of harm.

Performance (or optimal performance) can be defined as the degree to which individuals achieve a desired outcome when completing goal-oriented tasks. By the nature of its difficulty, an extreme environment like space commonly renders the completion of specific tasks much more challenging. Therefore, a smaller number of individuals may be capable of optimally performing a given task (Paulus et al., 2009; M. Schmidt et al., 2023)

Each of these three domains will have many specific measures. One of the HRP-C objectives is to continuously study how various factors affect each of these outcomes positively or negatively. The goal is to maximize each, while acknowledging there are often tradeoffs between them.

Commensurate with these objectives, the HRP-C intends to develop a Human Readiness Scale or a Human Activity Level Scale. This would be a set of quantitative measures built into a scale that assesses the readiness of any individual to enter into the space environment. This will help inform the preparation needs of the person entering space, as well as any additional training that may be beneficial to a given individual.

1.7 RESEARCH, CLINICAL, AND PERFORMANCE APPLICATIONS

The HRP-C is focused on research that is oriented toward the eventual (and timely) development of applications for spaceflight that provide *clinical solutions* and have *performance applications*.

In support of this, one aim is to encourage research teams to be composed of members that represent 1) domain specialist *scientists*, 2) domain specialist *physicians* and/or *other clinicians*, and 3) domain specialist *human performance* scientists. This will ensure that research will always be founded in rigorous scientific methods with careful attention to its clinical value in helping humans to thrive and perform in space. Fundamentally, research findings are intended to be evaluated for their application to clinical practice or enhancement of human performance.

2.0 ORGANIZATION OF HRP-C OPERATIONS

The operations of the HRP-C have been organized into three tracks which are complementary by design. Each track possesses its own unique implementation strategy. For cohesion, each track has a relationship with other tracks. They are intended to generate a comprehensive and growing data set that expands the knowledge pool that serves civilians entering space. The tracks include:

- Track 1: Comprehensive Measures, & Monitoring
- Track 2: Spaceflight Risks & Targeted Research
- Track 3: Operations, Programs, & Capabilities

Collectively, these form a foundation upon which a comprehensive HRP-C will be built. Their function can briefly be summarized as follows, with a more detailed description to follow in Sections 3, 4, and 5.

2.1 TRACK 1: COMPREHENSIVE MEASURES, & MONITORING

Track 1 research does not target specific diseases, exposures, or risks, but rather casts a wide net whereby signals and patterns can be detected across missions. These data are expected to lead to novel hypotheses and countermeasures. It is also a means to accelerate the rate of discovery. This track is designed to apply a comprehensive set of measures to as many of the commercial missions as possible. This allows for the comparison of high dimensional data sets across all missions, regardless of mission parameters or flight provider. The approach also enables the ability to compare missions across countries as other countries adopt this harmonized methods approach.

2.2 TRACK 2: SPACEFLIGHT RISKS & TARGETED RESEARCH

Track 2 is focused on known spaceflight-related medical and behavioral risks. The track is hypothesis driven, asking specific research questions that require validated, reliable, and sensitive measures and established experimental controls. Each study is funded through and is

executed by the team submitting the research proposal. The HRP-C Human Safety Risk Board (HSRB) will be central to establishing research priorities so that the more pressing problems of civilian spaceflight can be addressed in the timeliest manner. Note that the term spaceflight when used henceforth includes spaceflight and habitation.

2.3 TRACK 3: OPERATIONS, PROGRAMS, & CAPABILITIES

Track 3 establishes a set of fundamental capabilities necessary for a robust, rigorous, and sustained civilian research program. Track 3 is not a research track in and of itself. Rather, Track 3 is the backbone upon which the operations of Track 1 and 2 reside. This includes such things as an HRP-C HSRB, an institutional review board (IRB-C), space health reporting system (SHRS), human specimen biorepository, civilian spaceflight data repository, historical archive, and others. Track 3 will also contain a dedicated effort to translate space-related discoveries into Earth-based clinical medicine applications, so that the benefits of these space-directed expenditures will feed back to Earth in a formalized manner. These Tracks and their relationships are depicted in Figure 1.

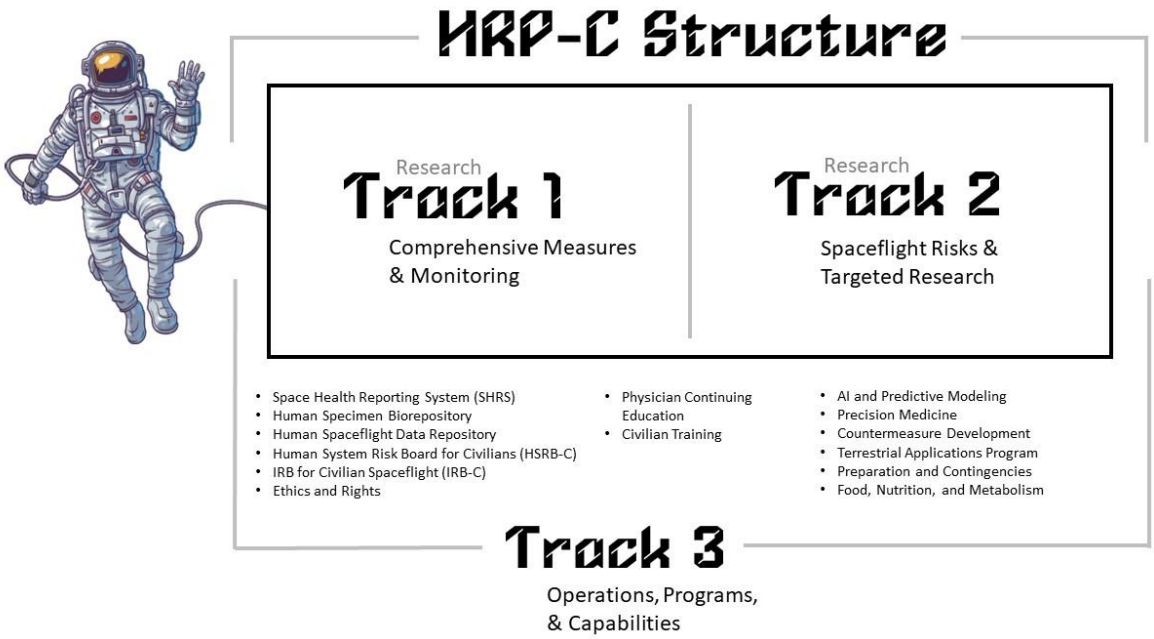


Figure 1 HRP-C Structure Tracks 1 and 2 are research tracks. Track 3 is focused on operations and capabilities, which underlie and support all research activities.

3.0 TRACK 1: COMPREHENSIVE MEASURES & MONITORING

"…to know that we do not know what we do not know, that is true knowledge"

- Nicolaus Copernicus

The *Comprehensive Measures & Monitoring* Track is intended to supply knowledge about the unknowns of civilian spaceflight risks and benefits. This research will leverage sets of measures that can be deployed across all commercial spaceflight missions, regardless of flight provider or flight profiles (Design Reference Mission; DRM). The measures and methods are intended to be harmonized across missions enabling the ability to compare missions with widely variable civilian populations, vehicles, habitats, distance, duration, and design. This approach will provide the most comprehensive mapping ever undertaken of humans in space, which will result in accelerated development of medical tools to help people live, perform, and thrive safely in space and potentially on Earth.

Comprehensive measures differ from *standard measures*. In principle, standard measures consist of a minimal set of important measures applied to all space missions that do not focus on one particular physiological system but look at all of the systems at once. While standard measures are robust, they generally do not include multiomics molecular measures, extended physiological measures, or extensive behavioral measures at the depth proposed herein. Importantly, comprehensive measures, by virtue of their extensive feature diversity, are expected to identify new targets (measures) that may one day be incorporated into the *standard measures* suite.

The extensive breadth of these *research* measures is expected to provide the following benefits:

- Accelerate the rate of discovery on space missions by building the most comprehensive set of untargeted (see definition below) measures across multiple missions to date,
- Generate new hypotheses that serve as the basis for focused research in Track 2,
- Generate novel countermeasure targets for countermeasure development,
- Provide insight into new biomarkers that can be added to the *Standard Measures* package that becomes a part of the *clinical* assessment on all missions, and
- Provide the most comprehensive assessment possible when new medical countermeasures are being tested through targeted research.

Categories of Comprehensive Measures and Monitoring

1. Molecular Phenotyping*
2. Physiological Phenotyping
3. Behavioral Phenotyping

4. Morphological Phenotyping
5. Environmental Phenotyping

**Phenotyping* is defined as the process of determining, analyzing, or characterizing the observable characteristics of an entire human or of selected domains of a human, including its environment.

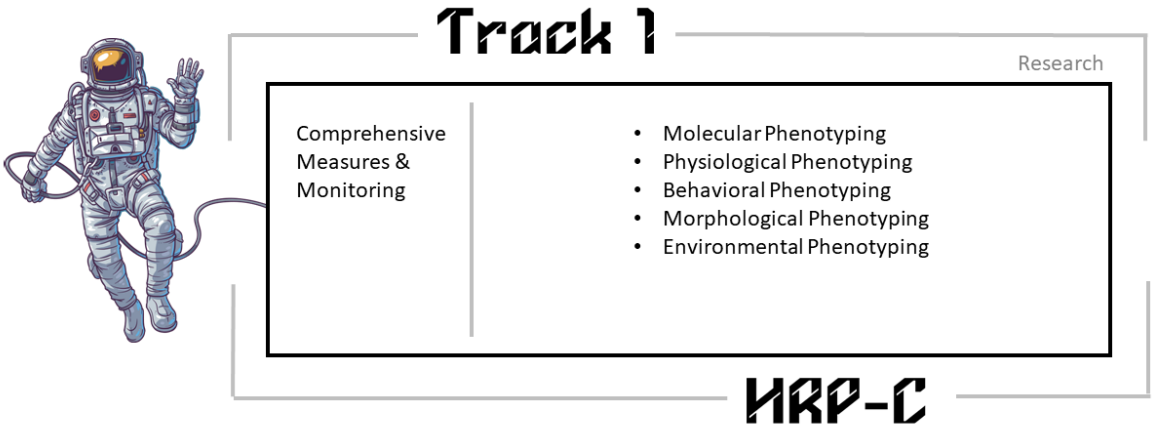


Figure 2 Comprehensive Measures and Monitoring Track 1 is intended to capture the widest possible number of measures across flights and providers. Using harmonized methods, this will be an opportunity to compare humans of differing phenotypes engaged in missions of different parameters, so that robust comparisons can more easily be made. From this data, novel hypothesis and novel countermeasure targets are expected to be developed.

3.1 MOLECULAR PHENOTYPING: MULTIOMIC MOLECULAR MEASURES

Background

The term Omics refers to the comprehensive analysis of a particular class of molecule or biological component, typically at a large-scale level. The level of molecular detail captured

allows one to more clearly describe the structure, make-up, and function of a given biological system. It is characterized by the use of high-throughput techniques, such as genomics, proteomics, metabolomics, and transcriptomics, to study the entirety of a specific category of biological molecules within a civilian space traveler. These techniques allow for the gathering of vast amounts of data to better understand the structure, function, and interactions of these molecules through bioinformatics analysis.

Multiomics refers to a combined assessment of several of these individual 'omes/omics' (molecular categories) at once. Table 1 lists each of the common omics measures with a brief description. The compendium of multiomic measures is referred to as the molecular phenotype. Phenotype refers to the observable characteristics of an organism like a human (e.g., an observation of the molecular features).

One of the features of omics (and multi omics) is that the approach is *untargeted*. Untargeted means that rather than predetermining which molecules will be measured in an experiment, the fullest complement of molecules is measured. This differs from *targeted* analysis, whereby the molecules to be measured are *preselected* and often far fewer in number. The limitation of targeted analysis is that there is vast molecular activity that could be taking place outside the molecules that have been chosen in a given experiment and will therefore be missed. Thus, in targeted analysis, the investigator has to 'guess correctly' that the molecules chosen for analysis are the ones likely to be involved.

Untargeted multiomics solves this problem by casting the widest possible molecular net. It presupposes that we do not fully understand all the molecular dynamics in a given condition (e.g., spaceflight; countermeasure). Therefore, we capture the vast landscape of the molecular networks and search for patterns of variance (change). These new patterns are the source of new hypotheses and new countermeasure targets. This can speed discovery considerably and accomplish in fewer years what targeted analysis may take many years through sequential targeted studies to reveal. In practice, targeted analysis may measure dozens of molecules, while untargeted analysis routinely measures hundreds to thousands to tens of thousands of molecules.

There is an extensive body of terrestrial medicine literature regarding the analysis of omics and their relation to terrestrial diseases. There is now a small but growing body of literature (e.g. NASA Twins Study and Inspiration 4 mission) that details the molecular patterns in cells, tissues, organisms, and human subjects entering the spaceflight environment. For example, multiomic assessment on the NASA Twins Study, showed significant alterations in the epigenome, genome, transcriptome, gut microbiome, plasma proteome, metabolome, among others (Garrett-Bakelman et al., 2019; Gertz et al., 2020; M. Schmidt et al., 2020a; M. Schmidt et al., 2020b). The

Twins study also showed us what was not changing in space and what persisted (and for how long) upon return to Earth. Quantitative measures of Omics provide important insights into the etiology of such conditions, while also providing insight into preventive and therapeutic strategies.

The SpaceX Inspiration 4 mission represents the most comprehensive multiomics analysis published to date (Houerbi et al., 2023; Kim et al., 2023; Mason et al., 2023; Overbey et al., 2023; Park et al., 2023; Tierney et al., 2023). Similar methods have been applied to ongoing missions such as Axiom 2 (analysis in process), Polaris Dawn, and others.

The utilization of Omics assessments in the spaceflight environment can be used to ask and answer non-hypothesis-driven and inductive questions about the response to spaceflight on the molecular level and how biological systems transition into and out of that environment.

Table 1 Battery of Omics with a Brief Description Each individual cell below represents a specific form of omics. For instance, assessment of the whole genome is termed *genomics*. Assessment of the small molecule pool (metabolites) is termed *metabolomics*. When more than one of the 'omics' below are measured together it is termed *multiomics* (M. Schmidt et al., 2016).

Measure	Description
Genome	The DNA exome, including single nucleotide polymorphisms, copy number variants, insertions, and deletions.
Epigenome	Transcriptomic regulating factors not empirically coded in the genomic sequence, including methylation and acetylation
Transcriptome	Assessment of gene expression through RNA transcripts
Proteome	The entire collection of proteins found in a particular cell type or body fluid under a particular set of environmental conditions such as spaceflight. This includes post-translational modification of proteins
Metabolome	Collection of all low-molecular-weight molecules (small molecule metabolites <1500 amu) present in a cell, tissue, or body fluid that are participants in general metabolic reactions and that are required for the maintenance, growth, and normal function of a cell

Microbiome	The microorganisms, including bacteria, archaea, fungi, and viruses that live in the digestive tracts of humans (gut microbiome). The gastrointestinal metagenome is the aggregate of all the genomes of the gut microbiota. Functional microbiome genes are those genes responsible for microbial metabolism in the gut. The skin, nasal, oral, vaginal, and other microbiomes are important but represent the site of other microbiota in humans. Further, the microbiome of the spacecraft or habitat can be analyzed and correlated with the human microbiome
Immunome	All the genes, proteins, and other molecular features that constitute the immune system
Exposome	Environmental exposures that an individual encounters throughout life or during specific exposures, and how these exposures impact biology and health

Impact

Characterizing the molecular phenotype via a multiomics approach will yield several immediate and long-term results:

- In the short term, the comprehensive nature of omics measures will allow for untargeted assessment of critical data from multiple body systems associated with known problems of spaceflight. These assessments can be correlated with the known physiological, behavioral, morphological, and environmental features.
- In the long-term, detailed analysis of these data will allow for multivariate pattern analysis from annotated datasets to help answer research questions aimed at preventative measures and countermeasure development when needed.
- Multiomic approaches will also help the spaceflight community understand the unknown landscape around entry into space, status in space during missions of variable duration, and entry back into an Earth environment.

STATEMENT OF WORK

- Expand the ability for absolute quantitation (vs relative quantitation) in multiomics sample analysis
- Expansion of analytical capabilities to isolate and identify greater numbers of compounds
- Development of increasing capability to obtain samples ‘in mission’
- Develop increasing capability to conduct sample analysis ‘in mission’
- Refine the capability for stable specimen storage and transport

3.2 PHYSIOLOGICAL PHENOTYPING

Background

The term physiological phenotype refers to the set of measurable outputs from physiological processes in the human body. While this term, physiological, often refers to multiple levels of cells, tissue, and organ function and the measurable signals generated from those processes, in this case, the term "physiological phenotype" relies heavily on the set of measurable electrical, sonic, optical, and other signals generated from physiologic processes in the body. Importantly, as civilian space travelers transition into, inhabit, and exit from the space environment their body generates multiple physiological signals from critical systems such as the cardiovascular, respiratory, and nervous system that are critical to understanding the body's status within its environmental context.

For example, during the transition into space, respiratory rate, body temperature, and pulse oximetry (the partial pressure of oxygen in the blood, pO2) can help the medical monitoring team at mission control assess how an astronaut is responding to heavy g forces and other factors. This understanding can help them assess performance and risk with a goal of implementing the necessary countermeasures, if needed. In the research context, gathering these data on an increasing number of participants can also help teams understand the variability in response associated with the spaceflight transition. It should be noted that the transition out of space presents many of the same problems as the transition into space, however, unique to the transition out of space is the mission duration and the myriad adaptations that have occurred during the time in space. This potential and the variability in response associated with it could lead to further unknown complications, which the medical community needs to be ready for.

Once an individual has reached space, measures of the physiological phenotype such as Finger Plethysmography (EndoPAT) and Sleep Score/Vigilance Testing can help medical teams understand how participants are adapting to the spaceflight environment to help them thrive. Similarly, the data gathered can help researchers understand the range of in-space adaptation phenotypes, which will lead to helping more humans live and work in space long-term.

Data about the physiological phenotype is additionally important in the context of other comprehensive metrics because its signals often represent functional processes within the body. By correlating these data with other measures, such as molecular phenotype, a much deeper understanding into how the human body responds to space is possible. This understanding could lead to an ability to build models (such as the astronaut digital twin) that can predict when an

astronaut is about to have a problem in performance and could help medical teams de-risk a mission before serious complications occur.

The following list of measures is an initial set of metrics that we propose need to be collected. Although not exhaustive, the list represents a set of core metrics that will be useful to a better understanding of the physiological phenotype in spaceflight.

Table 2 Selected Physiological Measures Below is a selected list of tests that can examine attributes associated with an individual's physiological phenotype. The summary should be seen as a very basic example of the types of physiological data that can be collected on all those operating in extreme environments. Assessment of the physiologic domain is complex and there exist numerous inventories that one should consider, so that the right tools are used for the cohort and the DRM. Thus, these methods merely represent a basic consideration.

Physiological Signal	Description
Heart Rate Variability (HRV)	HRV is the variation in time between successive heartbeats. It is a measure of the autonomic nervous system's influence on heart rate and can provide insights into stress, fitness, and overall health.
Respiratory Rate	RR is a direct indicator of pulmonary function and response to stressors, physiologic, psychological, and environmental induced.
Body Temperature	Body temperature is the measurement of an individual's internal temperature, typically in degrees Celsius (°C) or Fahrenheit (°F). It is an essential indicator of metabolic and circadian rhythms.

Blood Pressure (Pulse pressure)	Blood pressure is the force of blood against the walls of the arteries. Pulse pressure is the difference between systolic and diastolic pressure and is important for assessing cardiovascular health.
Pulse Oximetry	Pulse oximetry measures the oxygen saturation in the blood, often measured as a percentage. It is a vital parameter for assessing respiratory function and oxygen delivery to tissues.
Sleep Score/Vigilance Testing	Sleep scores or vigilance testing assess sleep quality, patterns, and daytime alertness. These tests can provide information about sleep disorders and overall sleep health.
VO2 Max	VO2 max (maximal oxygen consumption) is the maximum amount of oxygen an individual can use during intense exercise. It is a key parameter for assessing aerobic fitness and endurance.
Finger Plethysmography (EndoPAT)	Finger plethysmography, often measured with EndoPAT, assesses endothelial function by measuring changes in blood flow in response to stimuli. It can provide insights into vascular health.
Spirometry	Spirometry measures lung function by assessing the volume and flow of inhaled and exhaled air.

Actigraphy	Actigraphy involves wearing a device that measures movement patterns and is used to monitor sleep-wake cycles and physical activity. It is often used in sleep research and assessing circadian rhythms.

3.3 BEHAVIORAL PHENOTYPING

Background

Civilians will not only be participating in suborbital and orbital flights lasting from several minutes to hours, but they will also be living and working in space for weeks or months. Orbital stations and surface habitats will house engineers, technicians, maintainers, scientists, medical professionals, chefs, and service personnel. Many of their activities will be safety critical, including responding to emergencies, extravehicular activity (EVA), piloted rendezvous and docking, deployment of equipment, repair of equipment, etc. These workers will be exposed to high cognitive workloads and physical exertion including thermal stress, overuse injuries, and fatigue. Psychological, social, and cognitive issues could compromise the industry objectives and civilian safety by affecting the reliability and effectiveness of spacefaring civilian task performance.

Superimposed on the typical work-related stressors, such as high workload, see Figure 4), are many spaceflight stressors that can result in performance reductions including altered G forces, radiation, isolation, confinement, persistent danger, and physiological deconditioning. Space is a remote and hostile environment, civilians will be required to always reside within an artificial, closed habitat (i.e., interplanetary ships, orbiting station, surface dwelling, enclosed rover, extravehicular suit). These habitats are confining and do not allow the sensory experiences to which we are accustomed, such as a soft breeze on our face, birds chirping outside an open window, or the smell of fresh jasmine in a garden. In addition to being confined, spacefaring civilians will be separated from friends and family members. Return to Earth may be possible or a return journey could be delayed by months. Depending on the distance from Earth, communications with loved ones may not be frequent and anomaly resolution (problem solving) advice from Earth experts may be limited.

Scientific studies performed in space analogue environments such as Antarctic Stations, submarines, and in underwater facilities have found cases of depressed mood, anxiety, and anger

(Riva et al., 2022). Predictors of mood and performance include workload, personality, interpersonal needs, coping styles, a low socially coherent group, the diurnal cycle, and the severity of the physical environment. Not only can psychological reactions affect the individual's task performance, but they can lead to increased negative interpersonal interactions (Tafforin et al., 2015). If the space facility houses individuals from different cultures, then language, traditions, expectations, and societal norms will vary making everyday living that much more challenging.

Although it is unclear how space radiation affects human task performance, there is evidence that cognitive processing is affected in lower species (Ronca et al., 2019). An assumption that there may be cognitive deficits early in a space mission is based on anecdotal evidence from professional astronaut memoirs, lectures, and journals. The following excerpt from one astronaut's personal journal (Stuster, 2010) represents a commonly reported decline in cognition:

> "Not sure if the short term memory is reduced in space but I think it might be. I see little things like this on a daily basis with me and my crew mates. Little details that seem so trivial bite me all the time here" (Stuster, 2010)

Many Shuttle astronauts reported a decline in their ability to perform well-practiced procedures or even to add two simple numbers. As a mitigation they reported following their checklists or procedures more meticulously or using a backup crewmember to check their work when going through critical steps in a procedure.

Declines in human cognitive performance during spaceflight have been shown in some of the research literature, but it is not conclusive. Beard (2020a) discusses the difficulties in capturing cognitive changes using standardized tests including that the sensitivity of some of the currently used sub-tests (which measure selected features of cognition) was determined on populations with gross cognitive deficits like schizophrenia, severe depression, or other mental issues (Beard, 2020a). It is likely that spaceflight induced cognitive changes are gradual and subtle--that decrements have often not been empirically verified (which counters subjective reports and evidence). This does not mean that cognitive changes do not occur. Rather it suggests that we must rethink the standard cognitive sub-tests.

Although orbital and analogue results may be extrapolated to civilians living and working in space, unknown stressors will arise making predictions of psychosocial adaptation difficult. The psychological make-up and stress experiences of civilians will be more diverse. Prolonged exposure to these stressors could preclude performance of useful work. It is with diligently collected data that we may proceed ensuring the health and safety of individuals who venture into space.

Early and regular measurements of psychological, social, and cognitive performance - along with anonymous reporting - will help to quickly orient behavioral investigations and the provision of inflight psychological countermeasures and care.

Table 3 Sample Psychological, Social, and Cognitive Measures Below is a selected list of tests that can examine attributes associated with an individual's behavioral phenotype. The summary should be seen as a very basic example of the types of behavioral data that can be collected on all those operating in extreme environments. Assessment of the behavioral domain is complex and there exist numerous inventories that one should consider, so that the right tools are used for the cohort and the DRM. Thus, these methods merely represent a basic consideration.

MOOD	
Measure	**Description**
Subjective Stress	Perceived Stress Scale (PSS)
Depression & Anxiety	Depression, Anxiety, and Stress Scale (DASS-21)
Social Skills	Social Skills Assessment for Adults
Sleep	Sleep Disturbance and Sleep-Related Impairment (PROMIS)
COGNITION	
Attention	Complex Attention Sustained Attention
Sensation & Perception	Visual Acuity (Static/Dynamic) Contrast Sensitivity

	Proprioception
Working Memory	Dual-task Performance n-Back Abstract Matching Cognitive Flexibility
Procedural Knowledge	Reasoning, Decision-Making, Problem-Solving
Fine Motor Skills	NASA Fine Motor Skills Test Battery (although many FMS can be calculated from other visuo-motor tasks on this list)
Resilience	Connor-Davidson Resilience Scale (CDRS-10)

Each of the measures listed above imposes a study (mission) burden, given the time needed to complete them. The HRP-C should also pursue the use of sensitive and reliable non-invasive diagnostic performance measures. Some possibilities are listed in Table 4.

Table 4 Measures of Stressor Effects and Measures of Civilian Performance

Stressor Effects	Example Measures of Civilian Performance
Alertness	Eye Fixations
Attention	Eye Movements
Serial Choice RT	Keystrokes
Activity Level	Motion Detectors/Wrist Actigraphy
Visuo-motor	Keystrokes/MPT
Information Seeking	Eye Movements
Complex maneuvers	Glove or Control Sensors/Lunar Vehicle Steering Sensors
Outlier Detection	Eye Movements
Headache	Monitor Medications

Increased Fatigue	Activity Speed
Increased Heart Rate	Wrist Actigraphy

STATEMENT OF WORK

- Identify a novel, sensitive, and valid set of measures to detect subtle, yet significant changes in cognition.
- Validate non-invasive measures of psychological, social and cognitive measures

Leadership and Oversight

This work should be led by a trained cognitive and experimental psychologist or psychiatrist familiar with spaceflight effects on human behavior and the rigors of experimental design. It will be important to have clinicians deeply involved in such investigations, given that the eventual outputs are intended to serve clinical and performance applications.

3.4 MORPHOLOGICAL PHENOTYPING

The term morphology refers to structure and form, while the term phenotype refers to all the observable characteristics. Morphology encompasses the internal and outward appearance of a human space traveler (e.g., shape, size, pattern) as well as form and location of external and internal structures (e.g., bones, organs, soft tissue). Anatomy is a subsection of morphology.

There is an extensive body of terrestrial medicine literature regarding body composition and its association with diseases encompassing musculoskeletal, cardiovascular, endocrine, cognitive, and others. Quantitative measures of muscle, adipose, and bone provide important insights into the etiology of such conditions, while also providing insight into preventive and therapeutic strategies.

Moreover, differences in body composition can result in differences in tolerating extreme environments. This has been shown, for example, in the association with increased body fat and poor heat tolerance (Sawka et al., 2015; Alele et al., 2021). Of interest, research on the ISS has shown that those able to do the greatest number of push-ups and pull-ups while on Earth demonstrate a 29 to 39% reduction in viral reactivation while in space (Agha et al., 2020). While this form of fitness is not a specific demonstration of morphology (e.g., muscle mass), it is a reflection of muscle strength and endurance associated with muscle. It may one day become imperative that, in order to reduce infections in space, one has to optimize muscle mass, strength, and fitness as a preparatory measure (though this requires further investigation).

Related to the above, the concept of *reserves* is critical in human spaceflight. This is because the loss of bone and muscle in space may impact an individual with low baseline bone and muscle reserve differently than it may impact an individual with optimal or high bone and muscle reserve. This concept of reserves may even impact such things as cognitive function, since isolation studies in analogs such as Antarctica have shown volume losses in structures like the brain's hippocampus (memory center) to be as high as 7% after 14 months (Stahn et al., 2019).

Understanding body morphology, body composition, and reserves entering the space environment may become central to optimizing the space experience, but also to improving the human response once living back on Earth. This, therefore, impacts everything from training and mission preparation to post-mission recovery. The concept of reserves may become especially important in civilian space travelers, especially those who are already battling progressive bone and muscle loss caused by neuromuscular and musculoskeletal disorders. There is reason to consider that entering any high load stressor environment with greater bone, muscle, cognitive (Mullenax & Beard, 2022), and other reserves act as a buffer against loss when engaged with the stressor load. It may, therefore, become important to build up reserves to the greatest extent possible leading up to missions. This may offer additional insights into training and preparation programs, though additional study is warranted.

Beyond body composition, it is anticipated that some entering the spaceflight environment may have disabilities, body deformities, limb abnormalities, missing limbs, surgeries that impact body morphology, or prosthetics. Fully characterizing these features will be important to optimizing the experience for those entering space today but also to those entering space in the future, as more evidence is gathered.

Measurements associated with the morphological phenotype will be routinely collected pre-mission and post-mission. In-mission measures will be collected to the extent permitted by the flight providers and civilian space travelers in accordance with the mission parameters. These measures will be analyzed in context with all other phenotypic measures. Measurements include, but are not limited to visceral fat, subcutaneous fat, hepatic fat, intramuscular fat, fat-free mass, muscle mass, bone mass, bone density, and others.

Impact

Characterizing the morphological phenotype will yield four immediate insights into civilian space travelers:

- Afford the ability to assess at a detailed level the role of morphology (e.g., body composition, etc.) in the civilian's response to space and correlate with other comprehensive measures

- Better prepare one for entering the space environment by optimizing body morphology/composition for space
- Mitigate adverse sequelae upon return to Earth by having optimized morphology/body composition pre-mission.
- Advance training programs for civilians in space by providing more granular data about how morphology impacts humans in space and greater precision in training methods for individuals

3.5 ENVIRONMENTAL PHENOTYPING

Background

Human health, safety, and performance in space is reliant on the environment in which astronauts inhabit during all stages of the mission. Habitation systems include life support, environmental control, radiation protection, and exercise and health maintenance. Habitation modules are the structures that house astronauts and the habitation systems including the spacecraft, space station, and the spacesuit. From liftoff, throughout the duration of the mission, upon reentry, and through the final stages of landing, understanding the immediate environments that house astronauts are of the utmost importance. Systems that contribute to the habitability of the immediate surrounding environment include gasses onboard (O_2, N_2, CO_2, etc.), volatile organic compounds (off-gassed materials), radiated dust, and microbial communities, among others.

Impact

Each of the comprehensive measures above has a specific purpose, which is to characterize a discrete set of biological responses so that scientists and clinicians can 1) better characterize the biological response of civilians in space and 2) continue to develop optimal solutions to enhance the health, safety, and performance of civilians in space.

The environment in which the civilian space traveler operates has a strong influence on this response. When great detail about that environment can be captured, it can be compared with the other phenotypic measures noted above in order to better describe how different environments impact the civilian space traveler. This ‘environment’ takes two forms. One includes the mission parameters (DRM), which refers to such factors as g forces, distance from the sun, radiation, duration in space, etc. The other includes breathable air (e.g., CO_2 levels) and other environmental exposures, such as microbes that may inhabit the spacecraft.

4.0 TRACK 2: SPACEFLIGHT RISKS & TARGETED RESEARCH

The *Spaceflight Risks & Targeted Research* Track is focused on well-established risks that have been identified by NASA and other space agencies. This also includes specific space-associated conditions that have emerged as a high priority for research and countermeasure development.

The Track 2 discussion is organized around high priority risks observed in professional spaceflight that may have a particularly critical role in the health and performance of average civilians who possess more complex comorbid phenotypes.

1. Altered gravity, gravity transitions, and transient high g impact on health status of a large, diverse population of civilian space travelers
2. Space-encountered radiation impact on the physiology, psychology, and behavior of civilian travelers
3. Impact of spaceflight on individuals with implanted medical devices and prostheses
4. Isolation, confinement, and distance from Earth effects on the psychology and function of civilian travelers
5. Insufficient pre-flight familiarization, training, and medical preparation/logistics for anomaly response
6. Impact of spaceflight on civilian travelers from diverse populations with chronic health conditions
7. Impact of environmental exposures (e.g., dust, elevated CO_2, etc.) on the physiology and behavior of civilian space travelers

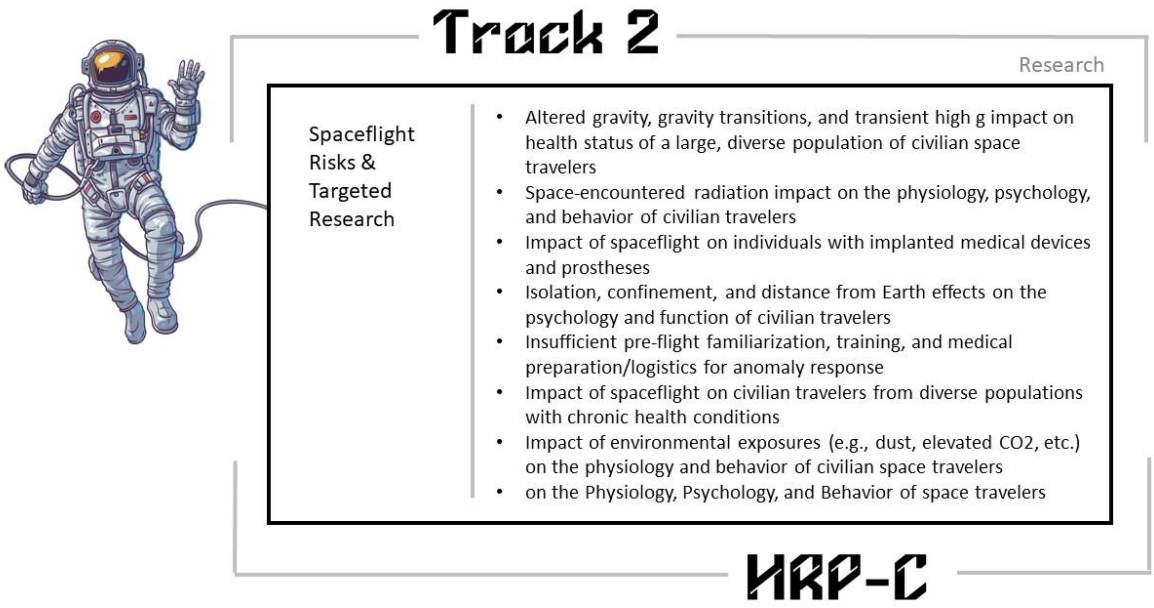


Figure 3 Track 2: Spaceflight Risks and Targeted Research Track 2 is focused on hypothesis-driven research to address specific research questions germane to civilian space traveler needs. A priority list of research topics (Section 4.6) is provided with the intent that these areas of research should be targeted immediately and not be delayed while awaiting the HRP-C operations to become fully operational. In the future, the Human Safety Risk Board (See Section 5.4) would be tasked with setting research priorities, which might be set directly by the HSRB-C or by a designee of the HSRB-C.

Funding of this research track is rooted in the submission of proposals focused on specific hypotheses, and specific measures or interventions seminal to the primary hypothesis. It is designed to ask specific research questions. The following summarizes each of the primary spaceflight risk domains with attention to the impact on a large, diverse population of civilian space travelers with potential comorbidities.

4.1 ALTERED GRAVITY EFFECTS ON THE CIVILIAN POPULATION

One of the five major space hazards identified by NASA are the effects of exposure to microgravity for humans in spaceflight and habitation. Here we are concerned with the potential effects of altered gravity on the health status of a large, diverse civilian population. Humans in space will experience three different types of gravity fields: (1) During space flight at distances where the gravity field is less than that of the Earth and where the traveler will experience weightlessness, (2) Long periods of exposure to microgravity on an orbital platform (the

gravitational field on the ISS is approximately 89% of that on the Earth's surface but objects in orbit are in a continuous state of freefall, resulting in an apparent state of weightlessness) or an installation on the Moon (1/6 the gravity field of Earth), and (3) Return to Earth where the human will have to readapt to Earth's gravity field.

With the prospect of expanding spaceflight and habitation for everybody, there is an urgency to understand more precisely the health and performance characteristics of a much larger and diverse population and implications for safe and healthy spaceflight and habitation. Informed by the NASA findings, we anticipate that many civilians are at greater risk for adverse health outcomes from exposure to gravity variations.

More than 50% of the U.S. population has one or more chronic health condition, such as arthritis, diabetes, atrial fibrillation, high blood pressure, asthma, migraine headaches, and kidney disease. One out of five individuals in the U.S. population have disabilities, such as cerebral palsy, spina bifida, spinal cord injury, multiple sclerosis, Parkinson's disease, hearing loss, visual disorders, brain injury, autism, and mental health disorders. Studies of people with these health challenges on Earth reveal major difficulties in attaining functional and cognitive independence and good quality of life. If they venture into space with these health and performance challenges, we need to examine the degree and magnitude of the challenges and seek effective countermeasures so that they can safely travel, live, work, and thrive in space.

The HRP-C is focused on the health, well-being, safety, and performance of civilians who will travel, live, and work in space in the coming decades. Although career astronauts show some adaptation with minor gravitational changes during space flight, it is clear that long periods of exposure to gravity variations can cause adverse symptoms and anatomical pathology. The following Table lists the major physiologic changes due to living and working during a space flight or space habitation in microgravity:

Table 5 Examples of the Major Health Effects Resulting from Exposure to Gravity Variations in the Professional Astronauts: Implications for the health of Civilians in Spaceflight

Category of Bodily Systems affected	Examples of Health Effects Associated with Exposure to Microgravity
Musculoskeletal conditions	Atrophy of postural bone and muscle with decreased bone and muscle mass, strength, and endurance without adequate exercise. (After the first month in space, bone atrophy occurs 10x faster and muscle atrophy 40x faster than occurs during the start of a sedentary lifestyle.)

Cardiovascular conditions	Cardiac muscle atrophy and change of the physical shape of the heart. (Aerobic exercise capacity is a measure of work performance. Without adequate exercise, aerobic capacity significantly drops.) Loss of hydrostatic forces with a fluid shift from the lower body upward to the chest, head, and neck (with facial swelling, full neck veins, and possibly causing eye, cranial nerve deficits and anatomical brain changes) (see SANS below) Risk for blood clots in the neck due to decreased venous blood flow. After landing the fluid shift may result in orthostatic intolerance (with light headedness leading to fainting.)
Neurologic conditions	Space motion sickness from vestibular system dysfunction occurs immediately on arriving in microgravity and during the initiation of gravity during the return to Earth and could last for hours or days post flight. It affects about 65% of astronauts. Early fatigue due to vestibular dysfunction Headache (from vestibular or SANS related) Spatial disorientation with: a. Loss of proprioception (loss of touch sensation and knowing where limbs are without visual cues) b. Decrease joint reflexes Space flight associated Neuro-Ocular Syndrome (SANS). (SANS occurs in 70% of astronauts starting about the 3rd month of space flight and consists of anatomical changes to the eye and brain. Visual impairment due to SANS induced eye anatomical changes.

	Body movement control on return to Earth may be disrupted for normal ambulation for 72 hours or more and control for driving or flying will be disrupted for several weeks (recovery of vestibular, proprioception and reflexes back on Earth.
Ear, Nose, Throat Conditions	Reduced smell and taste perception Hearing loss
Gastrointestinal and other abdominal conditions	Loss of gravity component for bowel motion. Change in gut microbiome organisms. Changes in bowel habits
Genitourinary Conditions	Renal stone formation due to bone atrophy Urinary retention (Neurologic changes)
Ophthalmic conditions	SANS induced eye changes including retinal folds, optic nerve edema, changes in vision, decreased eye pressure
Pulmonary and other chest conditions	Since all particles float in the breathing space atmosphere (in microgravity) it is possible that more foreign bodies will be breathed in and there could be increased Reactive airway/asthma and respiratory tract infections.

Knowledge about the effects of microgravity in low Earth orbit and beyond for those with known illnesses or on terrestrial medications who may be future spacefarers will be helpful to the space industry. Also, information about commercial space flight workers who are not required to undergo NASA's rigorous health screening before selection as an astronaut will support the industry's mission so they can maximize safety for those who travel into space. All categories of bodily systems impacted by space flight should be studied in a comprehensive program of human research.

Four of the key areas of human health affected by gravity variations are currently considered high priority by NASA include (but are not limited to): 1) Vestibular function, 2) Spaceflight-associated neuro-ocular syndrome (SANS), 3) Cardiovascular system, and 4) Musculoskeletal system.

4.1.1. Vestibular function: A primary effect of g transitions is on vestibular function. This is because one of the primary vestibular sensors – the otolith organs – transduces gravity. Inflight effects include space motion sickness (vertigo, dizziness, nausea, and vomiting), spatial disorientation, and lethargy. Postflight issues include these and ataxia (difficulties with posture and locomotion). Inflight issues can impact crew productivity but can generally be accommodated through scheduling and re-tasking, while postflight issues can be a significant safety concern if assistance is not available for spacecraft egress.

Many of these issues can be dealt with on an acute basis with medications (which are only partially effective and have side effects that can impede enjoyment and engagement in the flight experience). Currently, education and tempering of inflight expectations is the best course of action. Preflight experience with parabolic flight and centrifuge exposure assists in this effort for conditioning and preparation of the potential flyer. Research is needed to better understand how the aging increased potential for vertigo and hearing deficiency and medication use will affect these new spacefarers and what can be done to protect their health during space flight and return to Earth. Moreover, vestibular dysfunction in either the crew or others could be a safety concern; therefore, research for identification of crew motion sickness susceptibility and treatment that does not affect performance is important.

A high priority research project related to civilian vestibular function is to seek effective countermeasures for space motion sickness (SMS) for civilians with and without chronic health problems and disabilities.

4.1.2 Spaceflight Associated Neuro-ocular Syndrome (SANS): NASA's astronauts have experienced changes in their visual acuity after periods of three or more months living on the International Space Station (ISS). Though progress is being made, the reasons for the brain and eye changes in SANS have not been fully elucidated and no effective prevention or treatment is available. In addition to eye pathology including flattening of the back of the eye, swelling of the nerve entering the eye, and buckling of the eyeball, there are brain changes, possible cranial nerve damage (hearing, vision, smell, and taste) and decreased venous blood flow in the neck (and a least two reported blood clots). One hypothesis is that the microgravity induced fluid shift to the upper body increases intracranial pressure. Since SANS findings occur in 70% of astronauts with 20% having optic nerve swelling as well, civilian crews and similar surrogates should also be studied (and monitored as appropriate). For the civilian community who may have other aging or pathologic conditions, such research will be very important.

4.1.3 Cardiovascular system: In microgravity, the heart of astronauts change shape from oval to round, whereby heart muscles atrophy with reduction in the capacity to control constriction of the blood vessels and blood flow. Also, other factors change heart function. These changes are thought to be a major component in the development of SANS. Although arrhythmias have occurred during space missions, increased heart rhythm abnormalities in short duration spaceflight are not due to microgravity. Both benign and potentially lethal arrhythmias have been reported after longer duration in microgravity.

Deep vein thromboses (DVT) in the neck have occurred in two of NASA's astronauts; one in flight and one found retrospectively. The blood clot identified while the astronaut was on the ISS required blood thinner treatment during orbit. Current research and monitoring of the neck has

demonstrated left jugular vein blood flow to either be reduced leading to stagnation or clotting or the blood flowing backwards in the vein. In the aging less fit civilian community, DVTs may also occur in the legs if there is not sufficient movement of the lower extremities. Those who already have cardiovascular disease or arrhythmias and other aging or pathologic conditions may be at higher risk and appropriate AED or drug availability may be advised. Cardiovascular research (and, as appropriate, monitoring) will be very important for determining risk and safety needs in this population.

4.1.4 Musculoskeletal Systems:

During spaceflight, the human does not have the constant force of Earth's gravity (G) on the upright skeleton and the muscle of the trunk and legs no longer are required to work against the Earth's 1G. This causes both bone and muscle atrophy leading to less bone and decreased muscle strength. Although these changes could be considered "normal" for living in microG (μG), the individual would be at risk upon returning to Earth for the possibility of osteoporotic bone fractures and being unable to perform work due to muscle weakness and early muscle fatigue. It is unlikely that significant bone or muscle loss will occur within the first 30 days of space flight unless there are other underlying medical conditions.

Without adequate exercise astronauts can lose bone at an average rate of 1.5%/month starting after 60 to 90 days in μG; and trunk and lower extremity muscle mass loss can average 3%/month loss. Astronauts on space flight missions longer than 30 days are required to perform both aerobic and strength training. This program allows the crew to perform needed upper body work during extra vehicle activity (EVA) and to maintain their musculoskeletal integrity for their return to Earth.

Locomotion during space flight is done by pushing off with a finger and "floating" to the location desired; the legs are not used at all for normal locomotion. On the ISS walking and running are only doable on a special treadmill in which bungee cords (attached to the person's shoulders and waist and the treadmill base) pull the person onto the treadmill.

The effects of microgravity on civilians in spaceflight and space habitation becomes more challenging. Individuals with musculoskeletal disorders may experience health problems both inflight because of the μG increase in bone turnover and increased risk after their return to Earth. Those disorders include in part, Paget's disease of the bone, renal stones, vitamin D deficiency, use of high dose glucocorticoids for treatment of asthma or other conditions, early menopause, osteoporosis or osteopenia, amputees wearing protheses, and spinal stenosis. Individuals with limitations of movement due to cerebral palsy, muscular dystrophy, multiple sclerosis, atrophic lateral sclerosis, spina bifida, spinal cord injury, and other medical conditions could also have a

higher musculoskeletal health risk. Increased bone turnover during space flight may lead to de novo or new renal stones.

Current and approved therapy for astronauts includes adequate aerobic and strength training and the use of terrestrial antiresorptive medications used for the treatment or prevention of osteoporosis and osteopenia. Although both of these modalities could be used on a civilian space flight population, individuals with the disorders noted above will experience greater risk of renal stones during space flight and be at even greater risk back on Earth for fractures due to already being medically compromised. Research is needed to determine both the level of risk for the civilian population and the most effective strategies and interventions that will prevent changes in health in older, less fit and in special populations.

Research about the effects of microgravity is needed to determine risk and safety level for civilian participants, especially for those with underlying health conditions and disabilities.

The HRP-C will address the potential adverse effects of gravity variations and transitions and seek effective countermeasures for travelers with and without chronic health problems and disabilities.

4.2 SPACE-ENCOUNTERED RADIATION IMPACT ON THE PHYSIOLOGY, PSYCHOLOGY, AND BEHAVIOR OF CIVILIAN SPACE TRAVELERS

Civilian space travelers will encounter higher daily radiation doses than those living terrestrially. How and if the increased radiation exposure will affect travelers' health could be an important issue for the commercialization of low Earth orbit, cislunar space, and the lunar surface. Radiation is a major concern when traveling outside the Earth's protective geomagnetosphere. For example, on a mission to Near Earth Asteroids or Mars, radiation exposure can have many biological effects, including mutagenesis leading to the induction of cancers, and is listed as one of many environmental, nutritional, and other potential etiologies of cancer (Jones et al., 2018a, 2019).

In the United States, 18-23% of lifetime deaths are cancer related. Approximately 40% of people will be diagnosed with cancer at some site at some time during their lifetime. Individuals employed in space travel should be considered "radiation workers" because of the increased radiation exposure from all three main sources of space radiation. There are other potential radiation-exposure effects that pose concern, including potential central nervous system dysfunction, cognitive degradation, and vascular fibrosis, that are known to occur with higher dose and dose rate exposures, such radiation therapy and nuclear sources (Jones et al., 2019; Reddy et al., 2022).

Although space radiation will be substantially higher for civilian space travelers compared to those protected by the Earth, there is not sufficient epidemiological data to show that previous astronauts have a higher risk of death from stochastic conditions, such as cancer or cardiovascular diseases, due to their employment. There are data, however, to suggest that the radiation exposure has put them at higher risk of certain deterministic radiation bioeffects, such as lenticular opacities, or cataracts (Cucinotta et al., 2001; Jones et al., 2007). Appropriate health research and monitoring may be necessary for all spaceflight workers and travelers.

Background

There are 3 principal sources of extraterrestrial radiation which include: 1) Trapped- principally electrons and other particulates trapped in the Earth's magnetic flux lines, 2) Solar- background solar wind and episodic Solar Particle or Proton Events (SPE), and 3) Galactic- Galactic Cosmic rays (GCRs) which are atomic fragments principally derived from pulsar, quasar and black hole ejecta and consist of elemental nuclei, including heavier elements such as iron which impart higher kinetic energy (lineal) (HZE) when traveling at relativistic speeds; and thereby causing greater biological impact. Trapped and solar source radiation is reasonably easy to shield against, while GCR is difficult and metallic shielding, such as aluminum space vehicle components can produce concerning secondary particles, such as neutrons, when impacted by HZE (Badhwar, 1997; Jones et al., 2019).

The radiation environment is dependent on the 11-year sun activity cycle. At solar maximal activity (solar max) in which the sun is at its highest activity (solar flares, etc.) decreases GCRs. For example, in LEO the radiation is composed of a mixture of charged particles, such as protons and electrons, including those from the South Atlantic Anomaly (SAA), GCRs, Solar Radiation/Energetic Particles (SEPs), and Albedo Neutrons. These particles can potentially damage electronics, leading to costly mission failures and could also affect human health.

The Earth protects the living inhabitants of the planet in 3 ways: 2P shielding- from the mass of the Earth stopping incoming GCR, the geomagnetosphere generated from the ferrous core, and the atmosphere- abundant molecular gasses which can absorb incoming radiation. When the organism leaves the relative safety of the planetary surface, then the risk of exposure increases, especially in the polar regions of the Earth where the magnetic flux lines converge. (hence the observation of aurora near the poles) The Moon and Mars also protect those on the surface, but much less than the Earth, due to the absence of the powerful magnetic field and the minimal to non-existence atmosphere surrounding both planetary bodies (*Department of Energy (DOE) and Nuclear Regulatory Commission (NRC) Collaborative Interactions with OSHA*, n.d.; Dixit, 2023; Jones et al., 2019).

The average radiation dose for a person on Earth is 3.6 millisieverts/year (mSv/yr). The radiation dose in low Earth orbit (LEO) is about 70 times and a lunar mission is about 135 times higher per day than for a person on Earth. Representative and estimated spaceflight radiation doses for astronauts on specific missions are Space Shuttle 41C, 8-day LEO mission - 5.6 mSv; Apollo 14, 9-day Moon mission - 11.4 mSv; International Space Station (ISS) 6-month LEO mission - ~160 mSv; and a 30-day lunar mission - ~41 mSv. A 3-year Mars mission radiation dose would be between 900 to 1200 mSv. (see Table 1 for relative dose comparisons; Jones et al., 2018b). The current NASA radiation standard, for risk of additional cancer death beyond what usually occurs on Earth, allows up to 600 mSv per career. (See Table 2)

Table 6 Typical Spaceflight-Related Radiation Exposures

Event or Limit	Radiation Dose Level
Skin dose aboard the ISS during Solar maximum	0.5 mSv / day
Skin dose aboard the ISS during solar minimum	1 mSv / day
Space Shuttle Average mission skin dose	~4.3 mSv / mission
Exposure during EVA with excessive South Atlantic anomaly passes	4.5 mSv / event
Skin dose to a Space Shuttle crewmember during the October 1989 SPE (no magnetic storm, no EVA)	10 mSv / event
Apollo 14 (Highest Skin Dose)	14 mSv / mission
Dose estimated during the October 1989 magnetic storm, from crew dosimeters aboard Mir	30 mSv / event
Skylab 4 (Highest Skin Dose)	178 mSv / mission
Exposure limit for U.S. astronaut in any 1-month period	250 mSv / month
Skin exposure during an EVA during a radiation	400 mSv / event belt enhancement
Annual exposure limit for U.S. astronauts	500 mSv / year

Values indicate approximate dose to the blood-forming organs unless otherwise noted.
Abbreviation: ISS, International Space Station; SPE, solar particle event; EVA, extravehicular activity.

Table 7a and 7b: Recommended Organ Dose-Equivalent Limits from Ionizing Radiation for Space Crewmembers

a. Recommended Organ Dose-Equivalent Limits from Ionizing Radiation for Space Crewmembers in Low Earth Orbit

Limits	Skin (Sy or Gy-Eq)	Ocular Lens (Sy or Gy-Eq)	Blood-Forming Organs (Sy)
30-Day	1.5	1.0	0.25
1-Year*	3.0	2.0	0.50
Career	6.0	4.0	1.0-4.0†

*1-year limits are not to be considered annual limits, i.e., not repeated year after year.
†The limit for the dose to the blood-forming organs varies according to age and sex.
Gy-Eq = Gray-equivalent
Source: NCRP Report No. 98 and 132

b. Dose Limits (in mGy-Eq or mGy) for Non-cancer Radiation Effects

Organ	30-Day Limit	1-Year Limit	Career
Lens*	1,000 mGy-Eq	2,000 mGy-Eq	4,000 mGy-Eq
Skin	1,500 mGy-Eq	3,000 mGy-Eq	6,000 mGy-Eq
BFO	250 mGy-Eq	500 mGy-Eq	Not applicable
Heart**	250 mGy-Eq	500 mGy-Eq	1,000 mGy-Eq
CNS***	250 mGy-Eq	1,000 mGy-Eq	1,500 mGy-Eq
CNS*** ($Z \geq 10$)	-	100 mGy	250 mGy

*Lens limits are intended to prevent early (<5 years) severe cataracts (e.g., from an SPE). An additional cataract risk exists
at lower doses from cosmic rays for subclinical cataracts, which may progress to severe types after long latency (>5 years)

and are not preventable by existing mitigation measures; they are deemed an acceptable risk to the program, however.
**Heart doses calculated as average over heart muscle and adjacent arteries.
***CNS limits should be calculated at the hippocampus.
BFO: Blood-forming Organs; CNS: Central Nervous System

Mitigating the effects of ionizing radiation exposure is crucial for the success of all space missions. Radiation shielding can be effective for solar radiation protection for both background solar radiation and solar flare activity based on the amount of shielding available. This information is currently known and is being used by NASA and the spaceflight commercial providers. However, spacesuits used in LEO or on the lunar surface will not have adequate shielding for workers.

In LEO, shielding from high levels of GCRs occurs due to Earth's size and magnetic fields, and on the Moon or Mars some shielding occurs based on their size. Additional GCRs shielding occurs during solar max and this would be a safer time for space travel. However, in space between the Earth and Moon and the Earth and Mars, there is no current adequate shielding for GCRs.

It is unlikely that (with adequate shielding for) solar radiation and solar flares will cause acute radiation health problems. Long term, radiation has been proven to induce cancer, cataracts, cognitive problems, and cardiovascular problems in some people. Although on Earth, high dose radiation is responsible for cancer, e.g., atomic bomb survivors or the development of new (other) cancers from radiation cancer treatment, low dose radiation (35.8-159 mSv annual dose) also is shown to be potentially carcinogenic, e.g., lung cancer from radon inhalation.

Other countermeasures to the biological effects of radiation can also be employed, especially for those travelers leaving the protection of the geomagnetosphere e.g., in cis-lunar space. These come in the form of radioprotectors, radiomodulators, and radiomitigators. A significant body of research in civilian space travelers can be devoted to optimizing the use of pharmacologic and/or nutraceutical countermeasures for radiation protection (Jones et al., 2018a; Jones et al. 2019; McLaughlin et al., 2017).

Impact

Terrestrially, radiation workers are individuals who, in the course of their employment, are likely to receive a dose of more than 1 mSv millisievert in a year above background level. Most Earth-bound radiation workers can be completely shielded from all but minimal additional radiation exposures. This is not true for civilian space travelers. Thus, all workers during civilian space missions will fall under the rules and regulations for radiation workers.

Personalized, active dosimeters could be worn by all crew members, which can provide them with immediate current and cumulative radiation exposure. This could also include alarms to

indicate when the dose rate (based on current local fluence and flux) could place the individual at increased risk and allow the civilian space traveler to make decisions about proximity to shielding, etc., which could allow them to exercise ALARA- keep exposures as low as possible.

Importance

Space radiation has the potential to shorten the career, quality of life, or life of space workers because of radiation-induced illness(es) or bioeffects on their organs, such as ocular lenses. Future concerns may limit the time and dose of space radiation exposure due to increased health risks. Both ethical considerations and health regulations will be important determinants. The potential impact of the HZE on the neurons of the brain and other components of the central nervous system is currently not well-characterized, making it difficult to quantitate the risk of either acute effects on cognition and memory or chronic effects on brain function. There are now limits placed on hippocampal exposure for astronauts (Jones et al., 2018b; Jones et al., 2019; Sihver et al., 2015).

STATEMENT OF WORK

- Radiation monitoring should be instituted for space workers during their employment.
- Individual radiation dosimetry data should be available to these workers during their lifetime.
- Measures of radiation susceptibility should be advanced
- Radiation countermeasure development should be prioritized
- A cancer registry of space workers should be established.
- These data should be available for research purposes to improve health risk projections.

Expected Outcome(s)

Radiation monitoring should improve the health of the individual workers and help maintain a robust space work force. Appropriate research will establish radiation risk profiles and help in the development of radiation standards for space. The new knowledge gained will also aid in the future development of improved, as well as nutritional and pharmacologic therapies.

Relationship to other topics

Space radiation will be a given for all space missions and any tissue damage that occurs due to the space radiation could contribute to the risk of other health problems.

4.3 EFFECTS OF ISOLATION, CONFINEMENT, AND DISTANCE FROM EARTH ON AVERAGE CIVILIANS

"The human factor is three quarters of any expedition."

Roald Amundsen

The history of exploration is littered with examples of serious psychological problems occurring in response to the isolation, confinement, and other stressors of expedition life. Accounts of Adolphus Greely's disastrous Lady Franklin Bay Expedition, from which only six of 25 returned in 1884, affected all subsequent polar explorers. The stories of insanity and cannibalism among the Greely party were known by the members of the Belgian Antarctic Expedition 13 years later when they became trapped in the ice and experienced a deep depression that killed one man and drove another to bizarre acts of psychosis. Roald Amundsen, who performed his apprenticeship as an explorer on that expedition, wrote later that, "insanity and disease stalked the decks of the *Belgica* that winter."

Perhaps most notable was the psychosis that disrupted the crew of Navy Seabees who were building the facility at McMurdo Sound in 1955-57 in preparation for the International Geophysical Year. That case occurred soon after isolation and confinement had been implicated in "brainwashing" during the Korean War and it led to a long program of research concerning adaptation to Antarctic conditions and expedition leadership, conducted by the US Navy. An emergency psychiatric evacuation during the International Biomedical Expedition to the Antarctic (IBEA) in 1981 is a particularly relevant example, because the group was composed of 12 scientists from five countries, a composition similar to what might be expected of future long-duration space expeditions.

The relevance of living and working at remote duty stations to what might be expected of space travel inspired Werner von Braun to look to Antarctic experiences when identifying possible sources of risk for his Mars Project. He contributed to a series of beautifully illustrated magazine articles that led directly to the creation of NASA in which he wrote:

> "I am convinced that we have, or will acquire, the basic knowledge to solve all the physical problems of a flight to Mars [sic]. But how about the psychological problems? Can a man retain his sanity while cooped up with many other men in a crowded area, perhaps twice the length of your living room, for more than thirty months? … Little mannerisms—the way a man cracks his knuckles, blows his nose, the way he grins, talks, or gestures—create tension and hatred which could lead to murder." (*Collier's* April 30, 1954 "Can We Get to Mars?" p. 26.)

Cosmonaut Valery Ryumin (1980) echoed von Braun's concerns 26 years later when he wrote of his Soyuz space station experience, “All the conditions necessary for murder are met if you shut two men in a cabin measuring 18 feet by 20 and leave them together for two months.”

Several instances of behavioral problems and interpersonal conflict have occurred during the first 23 years of ISS operations, but most have been minor and transient. Astronauts are screened and routinely assessed for behavioral issues (more so than for almost all other jobs) and they usually set “getting along” with crew and mission control as goals for their missions. However, conditions occasionally conspire to evoke latent problems (e.g., depression, anxiety), outbursts, and hostility during six-month ISS increments. The problems have not been serious because the personnel have been screened and the mission durations have been manageable. These assurances do not apply to civilian space operations or to future long-duration space exploration, during which “time” will be a factor that can compound a trivial issue into a mission-threatening problem. Recent incidents onboard commercial aircraft illustrate the possibilities for unhinged behavior during commercial space missions (e.g., attempts to open hatches and shut down engines while in the air).

Space analog research has discovered common issues and predictable behavioral responses to isolation and confinement. A few results are listed below.

- Trivial issues will be exaggerated.
- Equipment will break or malfunction.
- Weather will delay or cancel planned work.
- Good leadership will be more important than good habitability.
- Communications with headquarters will be strained, occasionally.
- Minor behavioral problems will occur, but serious problems are avoidable.
- Future space expeditions will more closely resemble sea voyages than test flights.
- Humans can endure austere conditions but perform better with good habitability.

The following mitigations have been identified from space analog and ISS research:

- Be prepared for casualties.
- Devote special attention to food.
- Provide private sleeping chambers.
- Establish a “spirit of the expedition.”
- Test, train, and simulate everything.
- “Live off the land” to the extent possible.
- Select qualified and compatible personnel.
- Design for redundancy *and* maintainability.

- Distribute stowage of supplies and equipment.
- Expect weather to affect everything (yes, Mars has weather).
- Ensure that the crew remains entertained and busy with meaningful work.
- Provide familiarization and special training concerning the effects of isolation and confinement.
- The details will be different, but most of the problems that will confront future space explorers are the same problems that troubled explorers in the past.
- It will be particularly important to screen civilian candidates for space missions *very* carefully for mental health problems. Development of such could become the subject of directed research under the HRP-C.
- It also will be important to design interior controls and displays on the space craft (e.g., hatches, propulsion, scientific equipment) in ways that eliminate the possibility of inadvertent activation by anyone, and the possibility of volitional activation by unauthorized persons.

Statement of Work

- Design interior controls and displays on the spacecraft (e.g., hatches, propulsion, scientific equipment) in ways that eliminate the possibility of inadvertent activation by anyone, and the possibility of volitional activation by unauthorized persons.

4.4 PREPAREDNESS FOR UNFORSEEN AND UNEXPECTED ANOMALIES DURING SPACEFLIGHT

NASA recently identified a critical risk to professional astronaut safety and mission assurance that describes a potential inability of crew to autonomously detect, identify, and respond to anomalies that may occur during a mission. This risk arose because, with further distance from Earth, there will be communication delays and disruptions that will impede reliance on the mission control center in time- and safety-critical situations. This risk is relevant to civilian space travelers who are not constantly under surveillance by Earth experts, such as lunar surface workers or orbital platform employees. The HRP-C portfolio should contain an effort to identify key anomalies that should be trained pre-flight, in-flight (just-in-time training), or supported by advanced decision support tools. An example of high priority anomalies are severe medical conditions.

The NASA HRP has identified 120 high priority medical conditions for astronauts on Artemis missions. This list (Blue et al., 2022), and associated requirements (Beard et al., 2023), were generated for healthy, high performing crew. It is unknown how this, rather large, list would

change for the civilian population. Practical considerations limit the quantity of medical supplies to launch, medical capabilities to include (such as decision support, procedures, etc.), and pre-flight training to provide for a particular mission. The HRP-C research will provide critical knowledge for vendors and medical specialists to decide what medical supplies, capabilities, preparation, and training will be required for particular flight profiles and civilian medical, psychological, and health characteristics. Vendors could leverage the NASA-developed IMPACT model to weigh the pros and cons of each decision (Lake et al., 2023).

Training in support of individual civilian psychological, medical, and health needs should occur before, during, and after spaceflight. Inadequate preparation and training will compromise the safety and optimal performance of civilians during emergencies. The sufficiency of training should be recorded within an anonymized reporting system (see Section 5.8), which can be used to inform urgently needed research. Knowledge gained will contribute to appropriate, effective training development, testing, and implementation, and overall management of civilian programs and strategy development aimed at optimizing the commercial industries goals.

4.5 IMPACT OF ENVIRONMENTAL EXPOSURES (E.G., DUST, ELEVATED CO2, ETC.) ON THE PHYSIOLOGY, PSYCHOLOGY, AND BEHAVIOR OF CIVILIAN SPACE TRAVELERS

There are a host of spaceflight and task-related stressors that can affect human health and performance (Figure 4).

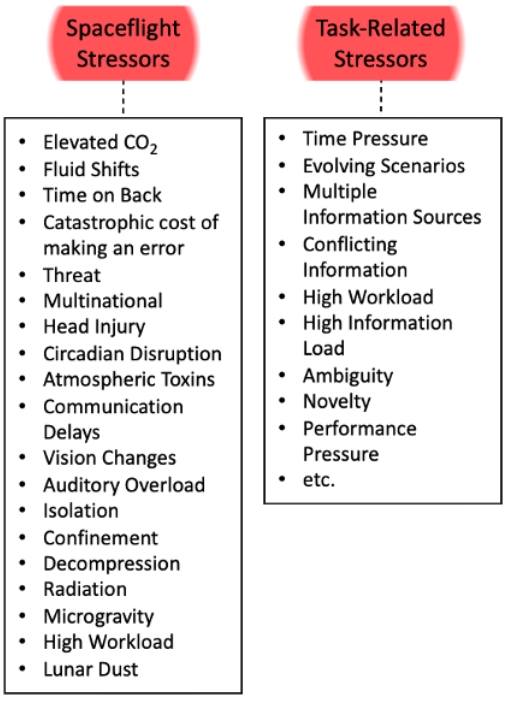


Figure 4. Spaceflight and Task-Related Stressors that Affect Crew Physiology, Cognition, and Motor Processes (Beard, 2020)

To simplify this discussion, this section will focus on only one spaceflight stressor: elevated CO_2. Long-duration spaceflight CO_2 levels are elevated relative to terrestrial levels because a tradeoff must be made between limits for ambient CO_2 and the increased power and supply required to maintain low levels of CO_2. As a result, spaceflight crew are exposed to CO_2 concentrations higher than Earth normal. The current outdoor Earth concentration of CO_2 is approximately 415 parts per million (ppm). CO_2 concentrations on the International Space Station (ISS) fluctuate in the 3000 to 5000 ppm range but can depend on such things as where a sensor is located, how many crewmembers are located in the node or module, activity level and experiment off-gassing. In microgravity, localized CO_2 pockets can form around a crewmember's nose and mouth in poorly ventilated areas. Carr found a positive correlation between reported symptoms and CO_2 level on ISS. ISS crews have reported headaches, may miss procedure steps, or have more difficulty finishing tasks on schedule when concentrations reach 3950 ppm (Carr, 2006). Law et al. reported that CO_2 level, crew age, and time in-flight were significantly related to headache probability. How chronic exposure to elevated CO_2 affects response to emergencies is unknown (Law et al., 2014).

There have been numerous recent summaries and reviews of elevated CO_2 effects on cognitive and motor function (e.g., Strangman et al., 2014). Some reviews focus on real-world situations, such as elevated CO_2 in classrooms, on submarines, in flight simulators, etc. Each review highlights the inconsistent and inconclusive results of the studies to date.

To tease out what the existing literature indicates about CO_2 effects on health and performance, with the goal of informing the setting of a Threshold Limit Value (TLV), Beard (2020b) plotted exposure duration as a function of CO_2 concentration (see Figure 5).

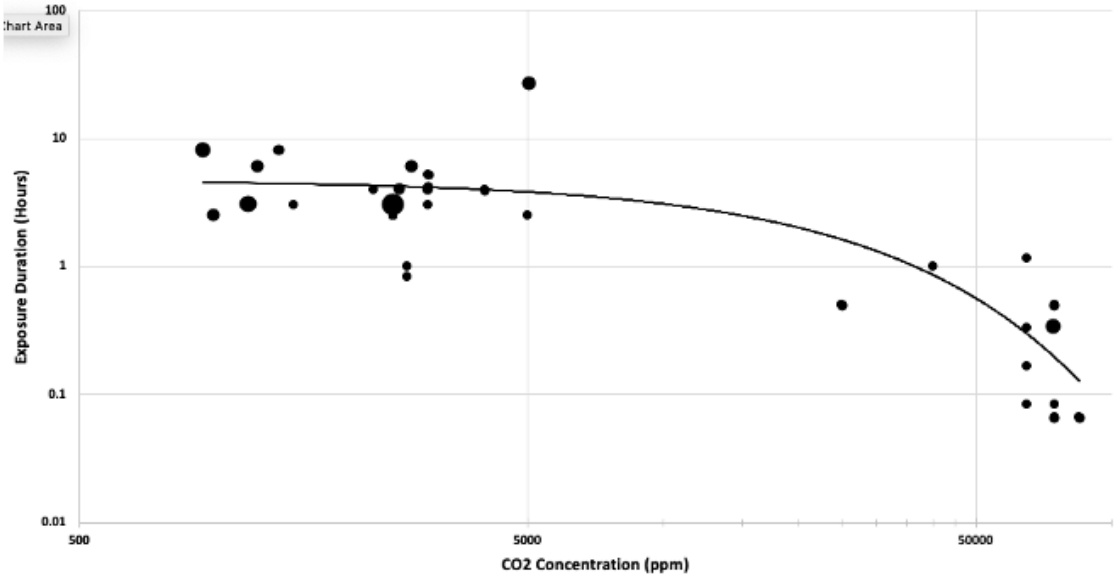


Figure 5. Studies Reporting a Significant Effect of Elevated CO2 on Cognitive or Motor Performance CO2 exposure duration (in hours) is shown as a function of CO2 concentration in parts per million (ppm). Because a wide range of durations and concentrations have been used in the literature, the axes are in log-log coordinates. Point size is an indicator of how many different cognitive or motor tasks were significantly affected by CO2. The largest point, for example, represents 6 tasks that were negatively affected at that exposure duration and CO2 concentration. The solid line is an exponential function fit to the data. (Beard, 2020b)

Unlike the published literature, an ISS crew's exposure is chronic. Similarly, civilians living and working in space will be exposed to chronically high CO_2. Astronauts appear to be hypersensitive to elevated CO_2 concentrations. Crew report symptoms, such as mood changes, performance changes, frustration, headache, and loss of concentration for CO_2 levels that are below spacecraft maximum allowable concentrations (Cronyn et al., 2012; personal communication with Flight Controllers).

As shown in Figure 5, the extreme environment of spaceflight involves additional stressors other than elevated CO_2. All spaceflight stressors can alter human health and performance. How they affect performance in concert is unknown.

STATEMENT OF WORK

- Monitor CO_2 concentrations during longer duration civilian spaceflights. The relationship between these concentrations and other performance and physiological data may then be ascertained. This will significantly advance our knowledge of CO_2 effects on average

civilians and help to set an empirically based Threshold Limit Value (TLV) for CO_2 in space habitats.

- Prioritize assessment of other environmental exposures**.**

4.6 PRIORITY AND URGENT HUMAN SPACE RESEARCH

Track 2 addresses hypothesis driven research that will be required to answer some of the pressing questions of research needed to enable civilians to live, work, and thrive in space. As noted, each risk will require individual research proposals that will be evaluated and funded based on the urgency of the problem being studied and on the merits of the proposal. The prioritization of this research will be established by the HSRB or a designated subcommittee of the HSRB.

It is important to note, however, that there are a number of medical problems that warrant immediate investigation, as determined by the expert group that founded the HRP-C effort. This is because 1) these problems currently persist as high levels of concern in professional astronauts and 2) the problems are expected to be amplified in civilian space travelers with comorbid health conditions and levels of fitness different than that of professional astronauts, and 3) the HSRB has not yet been assembled to set the initial research priorities.

Therefore, the list of priority projects that should be funded immediately include:

- Seek effective countermeasures for space motion sickness (SMS) for civilians with and without chronic health problems and disabilities.
- Identify treatable causes of and contributors to space-associated neuro-ocular syndrome (SANs).
- Continue to monitor civilian space travelers for SANs incidence, to better inform travelers and providers and better direct in-flight solutions (e.g., alternate eyewear).

- Study the effects of gravity variations and gravity transitions on the following body systems of civilians with and without chronic health conditions and disabilities for the purpose of creating countermeasures to mitigate the adverse effects:
    a. Cardio-vascular system
    b. Neuro-muscular and Musculo-skeletal systems to include:
        - Identify safe and effective means of preserving bone mineral density if an ARED-like device (provides a heavy load in an Earth-like exercise movement) cannot be accommodated in smaller spacecraft like Gateway.
        - Identify what characteristics of in-flight exercise best mitigate risks to immediate post-flight performance, especially among individuals with chronic health problems and disabilities

- Role of adjunct measures in maintaining bone and muscle in space: steroids, bisphosphonates, restricted blood flow, high-intensity interval exercise, muscle electrical stimulation.

- Study the effects of space radiation on the following body systems of civilians with and without chronic health conditions and disabilities for the purpose of creating countermeasures to mitigate the adverse effects:
  a. Cardio-vascular system
  b. Neurological system

- Investigate the effects of G forces on launch, during flight and return on the body systems, especially the skeletal and muscular structures, of civilians with and without chronic health conditions and disabilities for the purpose of seeking effective countermeasures to offset adverse outcomes.

5.0 TRACK 3: OPERATIONS, PROGRAMS, & CAPABILITIES

Conduct of research within the framework of the HRP-C requires a range of capabilities and programs that are not focused on individual research projects but rather are fundamental to operations. As such, the HRP-C must have organizational operations, programs, and offices that support the greater research efforts outlined in Tracks 1 and 2. These can be seen as a foundation upon which the entire HRP-C rests.

These operational capabilities are outlined below and are followed by more detailed descriptions of their nature, purpose, and function.

1. Space Health Reporting System (SHRS)
2. Human Specimen Biorepository
3. Human Spaceflight Data Repository
4. Human System Risk Board for Civilians (HSRB-C)
5. IRB for Civilian Spaceflight (IRB-C)
6. Physician Continuing Education
7. Civilian Training
8. AI and Predictive Modeling
9. Precision Medicine
10. Countermeasure Development
11. Terrestrial Applications of Space Research
12. Preparation and Contingencies
13. Food, Nutrition, and Metabolism

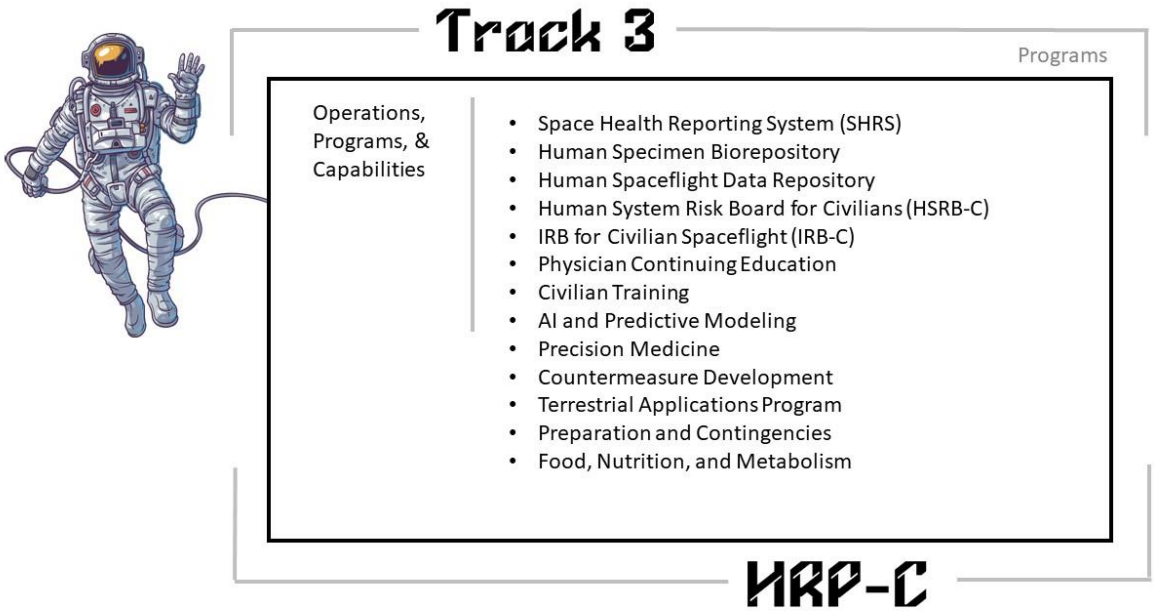


Figure 6 Operations, Programs, & Capabilities There are 13 elements within the Operations, Programs, and Capabilities Track. Though these will generate important data for the overall HRP-C, they are distinct from the dedicated research efforts of tracks 1 and 2.

5.1 SPACE HEALTH REPORTING SYSTEM

The Space Health Reporting System (SHRS) is intended to be a voluntary system by which individual adverse health signs or symptoms associated with spaceflight can be confidentially reported by crew or passengers to a secure central data repository. The SHRS is designed to provide another method for adverse health signal detection related to spaceflight. Functionally, this system would be similar to other safety surveillance systems common across many industries.

Adverse event (AE) is a term used in the medical, consumer, and regulatory environment to describe the emergence of symptoms coincident with exposure to a given product or substance. In the spaceflight environment, the term Adverse Health Experience is a more encompassing description that refers to any untoward medical *experience* occurring during the spaceflight

training, preparation, or flight period, whether it is associated with the mission procedures or not (Crucian et al., 2016). In spaceflight, the focus would be on *unexpected* experiences, since there are many challenging experiences in space that may result in signs or symptoms. However, expected experiences would qualify if they were of greater severity or duration than expected.

In comparison, the FDA Adverse Event Reporting Systems (FAERS and CAERS) are databases that contain adverse event reports, medication error reports, and product quality complaints resulting in adverse events that are submitted to FDA under both voluntary and mandatory adverse event reporting requirements. EPA has a similar system called the 6(a)(2) adverse event reporting system, which involves both mandatory and voluntary reporting of adverse effects. The SAHER will establish a comparable but more encompassing Space Health Reporting System to meet four specific objectives:

1) to provide spaceflight participants with a method to report any untoward clinical signs or symptoms believed to be associated with their inflight experience to a structured and reliable system; 2) to provide flight providers with a reliable means to monitor untoward events for the purpose of better understanding and predicting their passenger responses and to refine the ability to update methods; 3) to provide the scientific and medical community with human response data that further informs the development of tools of assessment and countermeasures for civilians; 4) to use these data to confirm the expected safety of spaceflight and enhance confidence within the populations that engage in spaceflight that there is a robust and effective method of identifying, managing, and mitigating safety issues before they impact public safety.

The commercial aviation industry participates in a similar program called the Aviation Safety Reporting System (ASRS), though it is not medically focused. ASRS **c**aptures confidential reports, analyzes the resulting aviation safety data, and disseminates vital information to the aviation community. This system is completely confidential, voluntary, and non-punitive. In the SHRS, reports are intended to be used to identify safety signals, enabling flight providers the opportunity to validate, investigate, and develop methods to mitigate adverse effects experienced by spaceflight personnel.

Adverse event systems can be either passive or active. In passive surveillance, the consumer or health care provider reports an adverse event of his or her own volition without prompting or being directed to a specific reporting system. This method is generally associated with a large underreporting factor. In *active surveillance*, the consumer is directed to a specific resource and is encouraged to report any untoward responses suspected to be associated with spaceflight.

The proposed SHRS program is intended to be an active surveillance program, wherein establishing causality based simply on the report of an adverse experience is not the goal. Causality assessment is more difficult than merely reporting or identifying signs or symptoms

believed by the reporter to be somehow associated with spaceflight. Use of the data collected through the system is expected to allow trend analysis to confirm or validate a safety signal that can be independently evaluated for its significance and need for mitigation. Therefore, in an effort to enable better reporting, causality assessment is left to a team of experts within the flight providers ranks as an internal matter. Whether these are shared with any outside party would be developed in a collaborative matter with confidentiality at the forefront of such considerations. In general, an SHRS is intended to be structured in a manner that benefits the corporate, as well as the space traveling community.

In addition to formal reporting, SHRS will incorporate civilian journal entries. In practice, journals would be kept separate from the SHRS, though they can be seen as companion data sets.

Space Journals

Stuster has led projects during the years 2003-2010 and 2011-2016 where he analyzed personal journal entries kept by 20 astronauts during their missions (Stuster 2016). These data provide metrics of critical behavioral issues such as workload, depression, anxiety, frustration, sleep, fatigue, and teamwork. Many crewmembers report that keeping a journal is pleasurable and that they look forward to entering their thoughts at the end of the day.

To demonstrate the value of a future Journals Flight Experiment for Civilians (JFE-C), statements from select entries of astronaut journals will be used (left column of the table below), along with how this statement may be used by HRP-C stakeholders (right column).

Table 8 Civilian Personal Journal Entries and Example Applications

Personal Journal Entry	Example Application
I have been waking up with a headache the first two days so I think I need to move my sleeping bag to a spot directly in front of a vent. I suspect CO_2 buildup.	Lessons learned that may be used for Civilian Training development (see Section 3.8)
I made far more little mistakes than expected. It always felt to me that my brain was not as capable up here. The reasons could be many, perhaps CO_2, 3D-world with no ceiling and floor, trying to juggle a thousand things throughout the day. Who knows. It really takes me a lot of effort to keep from making little mistakes.	Non-invasive indicators of cognitive status

I'm still amazed at how slow the mind is up here, especially when it comes to processing the details. I don't like the feeling that I have to read everything 5 times so I don't miss something	
Not sure if the short term memory is reduced in space but I think it might be. I see little things like this on a daily basis with me and my crew mates. Little details that seem so trivial bite me all the time here. Hopefully it will go away soon. I need to pay better attention to these little lessons that I seem to need to keep relearning. I do think I need to concentrate a bit harder up here than on Earth to avoid mistakes. I think my short term memory is reduced	Non-invasive indicators of memory deficits
Well, CO_2 is up to 3.0 and I can feel it. X is really feeling it. It is just one of those kind of annoying things that they don't really fix for us. They just ask us questions, How do you feel, but nothing ever changes with the CO_2. It's not terrible for me, but I do take a Motrin usually every day. And X is obviously feeling it too	Planning medical inventory needs

These few personal journal entries clearly demonstrate how introspective accounts of individuals who are living and working in stressful or unusual environments can provide useful information about the factors that affect individual and group performance under those conditions. To end this section on a bright note, the following provides personal journal entries categorized as "Wonderment". (Stuster 2016)

- Floating is awesome and the view is amazing. Can't believe we are here. [Day 1.]
- I love looking at the Earth and taking pictures. I love doing effortless and pointless somersaults.
- Had some good quality time in the Cupola. Words cannot describe the view and the feeling of looking back on Earth. I am definitely one lucky person to have this opportunity.
- I just saw the most amazing, most beautiful thing I have ever seen in space: Sun setting and throwing enormous golden rays of light across the entire planet. I am speechless.
- The reality of geopolitical and geographical differences among nations on the ground begins to fade as the greater reality of one species eking out a short life on this one

sphere while nestled at the far edge of an ocean of stars with their own planets and vast, glowing, eternally changing galaxies becomes the greater reality. It was just a few minutes, but I'll never forget it.

In the civilian spaceflight cohort that is expected to enter space with more complex comorbid conditions, there are three types of adverse events that are anticipated:

- Incidental events that may have happened anywhere, regardless of environment, context, or exposure
- Events where the space environment may exacerbate an extant clinical condition
- Events where off-nominal mission conditions exacerbate a normal or extant clinical condition

Confidential, Voluntary, and Non-Punitive

The SHRS program is voluntary in nature. It is hoped that the spaceflight providers see the benefit of constructing their own SHRS program in advance of any government regulatory effort. In this way, industry can take control of its own future by emulating some of the best practices that have been well established in other industries. It is also hoped that the greater participant number enabled by participation of all the flight providers will scale the N required to better detect patterns in this unique civilian flying cohort. In this way, any individual company can benefit from participation of other industry members. This, too, has proven successful in other industries.

Positive Findings Reporting Capability

One unique feature of SHRS in comparison to most adverse event reporting systems is the 'positive findings' reporting category in SHRS. It has been observed that selected clinical symptoms have shown improvement (albeit transient) when exposed to microgravity. This has been reported, for example, in individuals with disabilities who have flown on parabolic flights. For example, there are two case reports from parabolic flights where pain was substantially diminished during the variable gravity exposure. This unique element of the SHRS system is intended to capture such positive findings for the purpose of further informing the field about the impact of spaceflight across populations.

Impact

The SHRS system will provide a level of detail that is not easily obtainable by other basic forms of research. As such, it will afford a sensitivity to detecting emergent patterns of the human response to space that may not be captured by other forms of retrospective and prospective

research. It will also potentially provide early signals in people with comorbidities who fly into space, so that adaptive countermeasures can be more readily developed. This is a well-established means by which signals of an adverse response to Rx drugs, OTC drugs, and dietary supplements are detected in the community.

The benefit to the spaceflight industry will be three-fold. First, there is historical precedent for government regulators to refrain from regulation in cases where industry has stepped forward with suitable safety monitoring procedures. Thus, a strong industry SHRS may serve as prophylaxis against government regulation in this domain. Second, the data gleaned from a SSHRS program will enable industry to refine its methods and provide further confidence when providing informed consent. Third, with an organized industry program, consumers who have complaints will have a structured mechanism to which they can submit these complaints, which will be reviewed by a professional team. This is expected to generate enhanced consumer confidence.

Statement of Work

- Establish the guidance for SHRS
- Develop a central database and reporting infrastructure necessary receive and manage reports
- Develop a programmatic structure for flight providers
- Develop a suitable anonymization methodology so that confidential flight provider details can remain confidential
- Establish a reporting system that allows no-fault communication between human spaceflight organizations to improve safety.
- Develop a training program to train flight providers and clinicians in adverse event reporting
- Establish a SHRS Review Committee to review AE on a monthly basis

SHRS Review Committee Membership

- Chair: Physician trained in or experienced in adverse event management
- Representatives from commercial flight providers and other commercial spaceflight entities
- Representatives from NASA and/or FAA
- Representatives from the civilian population of individuals with and without chronic health problems and disabilities

5.2 SPECIMEN BIOREPOSITORY FOR CIVILIANS

The HRP-C will generate a significant number of human samples. The biorepository will play a crucial role in processing, preserving, and archiving specimens for biomedical research. The wide array of biospecimens (including blood, saliva, plasma, stool, urine, breath, skin, tissue, and purified components) maintained in the biobank can be described as a library of the human organism in space. Central to this effort will be rigorous attention to SOPs governing all pre-analytical steps. (Sanderson-November et al., 2022).

Spaceflight-derived biospecimens can be used for three primary purposes. First, immediate analysis can be conducted on the samples in accordance with a specific protocol approved by the IRB-C. Second, post-hoc analysis can be performed on the samples by the original investigators in accordance with approval by the IRB-C. Third, investigators not associated with the original study can petition the biobank for access to selected samples for a specific research purpose.

This latter use would occur by submitting a request to the HRP-C Biorepository Advisory Board, which would review such proposals for their scientific merit. Given the rarity of and difficulty of obtaining such specimens, such requests would be carefully considered, as they would naturally deplete the sample pool.

All such uses would be carefully governed by the IRB-C, so that fully informed consent is provided to civilian space travelers, and they understand the implications of storing and using their specimens for ongoing research.

In principle, there currently exist a small number of academic sites with biobanks holding civilian spaceflight samples from the major flight providers. These would be considered as early candidates to house such an HRP-C biobank, since they possess well-established procedures and infrastructure for such a program.

Impact

A central biorepository will ensure that specimens from civilian spaceflight missions are processed, transported, archived, and managed according to standardized protocols and methods. It will also provide a central location to which investigators can go to perform follow up research. The benefit is that sample viability can be assured by best practices. For scientists interested in follow up research, there will be only one or two central facilities to which they have to submit requests for the use of such specimens.

Features

Numerous regulatory considerations govern the proper operation of the biobank. This includes but is not limited to:

- The US Health Insurance Portability and Accountability Act (HIPAA)
- International Organization for Standardization, ISO 20387:2018
- The International Society for Biological and Environmental Repositories (ISBER) standards for best practices for managing (collection, handling, storage, retrieval, and distribution) of biological materials that are held in biobanks.
- The US National Cancer Institute (NCI) best practices to safeguard the quality of biological materials that are used for research
- The EU General Data Protection Regulation (GDPR) to safeguard the right to personal privacy
- The US 21 CFR Part 11 FDA-issued standard that directs the handling of medical records that are held in electronic form

STATEMENT OF WORK

- Establish the primary infrastructure conditions needed for a Specimen Biorepository for Civilians
- Establish the primary operational considerations needed for a Specimen Biorepository for Civilians
- Identify entities that currently operate civilian spaceflight biospecimen facilities, as potential candidates for the HRP-C biorepository
- Identify technologies that are necessary to address all the technical needs of a robust biorepository program
- Establish the HRP-C Biospecimen Advisory Board to review requests for use of specimens for post-hoc analyses

5.3 HUMAN SPACEFLIGHT DATA REPOSITORY

The breadth of civilian spaceflight is expected to include space tourism, travel to work at a destination, work while traveling, and will include both long and short durations in space. The mix of purpose, length of mission, variation in health factors, training of occupants, and vehicle type are all factors worthy of study as metrics of success are established in the industry.

Childress, Williams, and Francisco described the human system standards established by NASA that can serve all human space flight endeavors. NASA's Office of the Chief Health and Medical Officer (OCHMO) manages the standards that support astronaut health (NASA-STD-3001, Vol 1)

and specify requirements of vehicle design, operational requirements for safe human-system integration, and enable human performance (NASA-STD-3001, Vol 2; Childress et al., 2023).

These standards were developed for astronauts, a uniquely specialized, physiologically, and cognitively screened small population. The standards have been continuously improved and revised over the years via data collected across several missions. Commercial space flight operations will include a more heterogeneous population, diverse missions, varied training curricula, and human performance variation. Therefore, current NASA standards may not be directly applicable. Establishing and maintaining a human spaceflight database with operationally defined parameters is necessary to formulate standards for the new emerging operations. In addition, given the diverse pool of the civilian spaceflight participants, the effects of space with the potential diversity of underlying health conditions are unknown. Cataloging the impacts allows for tracking, proactive risk management, and leverage to support an inclusive opportunity for many civilians to travel and work in space (Marge, 2023).

As evidence of the benefits of collecting data across missions, NASA has several data repositories (e.g., NASA Open Data Portal). These datasets have informed missions over time. Creating a database that includes the varying missions, tasks performed, and metrics of performance allows for a data driven approach that helps the community inform each other of successful practices and areas warranting attention and vigilance.

The Commercial Spaceflight industry working with the Human System Risk Board and Institutional Review Board can establish a means for database development, variables of common interest, and portal criteria that protects the identity of participants while creating a repository for data mining, verification, and validation of commercial space flight human safety and performance standards.

These should at minimum include, characteristics of participants, crew design, and purpose of flight, human performance data, task, and mission performance. Information on crew composition, crew performance, and tasks performed would be beneficial. Logging duty time and details around issues such as fatigue are warranted. Considerations of spacesuit fit will be needed as participants will not resemble the typical astronaut of the past decades. Any details of mitigating risk and successfully addressing unexpected events would mirror other successful voluntary reporting programs such as ASRS. Any extravehicular activity will depend on a good alignment with human performance enhancing qualities in mind. Various companies will present different suits, protective gear, and sensor capabilities so it will be necessary to have a database to record the benefits and challenges. Data could be uploaded by each respective vendor, deidentified or identity protected, and protected from cyber-attack to allow for lessons learned, trending of data, and to showcase successful missions.

In September 2023, FAA's AST published Recommended Practices for Human Spaceflight Occupant Safety. The purpose is to suggest areas whereby industry can collectively determine how to manage identified risks during commercial operations. This is a good reference for industry to review and implement as it fits their profile and mission.

5.4 HUMAN SYSTEM RISK BOARD FOR CIVILIANS (HSRB-C)

5.4.1 The NASA Human System Risk Board

NASA manages the major risks to human health and performance through its Human System Risk Board. "The Human System Risk Board (HSRB) manages the process by which scientific evidence is utilized to establish and reassess the postures of the various risks to the Human System during all of the various types of existing or anticipated crewed missions." (*Human System Risk Board*, 2023).

NASA uses the Human System Risk Board (HSRB) to identify and track the major risks to human health and performance in space. It does this through a process based on continuous risk management (CRM). Potential risks are identified through previous flight experience, information provided by flight surgeons, and fundamental considerations of physiology. Each risk is assigned a rating based on its likelihood of occurrence (in a given DRM) and the consequence of its occurrence (loss of crew, loss of mission, long-term health impact). This provides an LxC rating. A "risk custodian" team is assigned to each risk; its task is to acquire information and update the risk ratings on a regular basis, by bringing the risk to the board on a regular schedule (or as needed if new information requires reassessment). The board discusses the evidence brought forward (in a standard format), and votes on the disposition of the risk (LxC).

Not all of the risks considered by the HSRB are allocated for research. HSRB does not dictate what the NASA Human Research Program takes on as research. Some risks are mitigated via engineering or operational changes, mission rules, or agency regulations. Some are waived by the Chief Health and Medical Officer.

The board is composed of representatives from the Human Health and Performance Directorate, the Human Research Program, the astronaut office, flight surgeons, and others. It meets regularly, and its intent is to review all of the risks in its domain each year on a continuous cycle.

The NASA HSRB recently adopted the use of Directed Acyclic Graphs (DAGs) as a way to capture and visualize the causal flow from spaceflight hazard (radiation, altered gravity, etc.), through physiological changes, to impacts on human health and performance, and mission outcomes (Antonsen et al., 2022).

5.4.2 Civilian HSRB

A civilian version (HSRB-C) should be a major component of a civilian spaceflight research program (HRP-C), with similar roles and appropriate modifications. The most important role of a HSRB-C is to provide a standardized, rigorous, and transparent mechanism for identifying, categorizing, and prioritizing risks. “Risks” in the case of CSRP might include those tracked by NASA through their HSRB (and addressed by NASA research). Some of these NASA risks might not be applicable to civilian spaceflight, and others would undoubtedly need to be added (including a large category of *preexisting medical conditions and their attendant complex therapeutics*, parsed into subcategories). Determination of the new risks would be the first order of business for a HSRB-C. Unlike the NASA implementation, the HSRB-C would in fact “dictate” where research (supported by the civilian HRP) would be needed.

5.4.3 HSRB-C Educational Outreach

One responsibility of the HSRB-C is to submit regular reports for public consumption that outline the HSRB-C findings. This allows the public to track the updates on risk assessment, as well as summarize positive findings and successes. Two tiers of reports are envisioned. The first is directed at the general audience. The second is more technical and directed toward scientific and medical audiences.

5.4.4 HSRB-C STATEMENT OF WORK

- Identify major risks for civilian spaceflight participants (as a function of mission, participant role, health status)
- Prioritize the severity of each risk (based on likelihood and consequence)
- Delineate status of each risk: requires research, tracking/monitoring, other
- Adopt a process whereby proposed risks are brought to the board for consideration
- Provide for continuous review of all risks
- Arrange for dissemination of board findings and research/monitoring results

5.4.5 HSRB-C Membership

- HRP-C leadership (director and assistant, chief medical officer, research director)
- Representatives from commercial flight providers and other commercial entities
- FAA/NASA flight surgeons
- Spaceflight participant representative

5.5 INSTITUTIONAL REVIEW BOARD FOR CIVILIAN SPACEFLIGHT (IRB-C)

The Institutional Review Board for Civilians (IRB-C) is the primary ethics committee formally designated to approve, monitor, and review biomedical and behavioral research involving humans. The key goal of the IRB-C is to protect human participants from physical or psychological harm, which is achieved by a strict process of reviewing research protocols and related materials. A second goal is to assure participant confidentiality, anonymity, and data privacy. The protocol review assesses the ethics of the research and its methods, promotes fully informed and voluntary participation by individuals capable of making such choices, and seeks to maximize the safety of participants.

In the United States, the Food and Drug Administration (FDA) and Department of Health and Human Services (Office for Human Research Protections) regulations have empowered IRBs to approve, require modifications in planned research prior to approval, or disapprove research. IRBs are responsible for critical oversight functions for research conducted on human participants that are 'scientific,' 'ethical,' and 'regulatory.' Similar organizations worldwide oversee human research, based on individual nation regulations.

The general practice of human spaceflight research must consider:

- Respect for persons: (1) individuals should be treated as autonomous agents, and (2) persons with diminished autonomy are entitled to protection.
- Beneficence: (1) do not harm and (2) maximize possible benefits and minimize possible harms.
- Justice: Who ought to receive the benefits of research and bear its burdens?
- Informed consent: assure adequate information, comprehension, and voluntariness
- Assessment of risks and benefits, including the nature and scope of risks and benefits,
- Assure participant confidentiality, anonymity, and data privacy

Impact

The IRB-C will ensure that the review of human research for civilians will be overseen by an ethics committee with spaceflight knowledge and experience. While there are many academic and commercial IRBs available to researchers, these are not generally familiar with the nuances of human spaceflight. Moreover, the IRBs that do possess spaceflight expertise are generally focused on professional astronauts. While these IRBs are fully capable of reviewing protocols focused on civilians, the HRP-C IRB will be an ethics committee dedicated to human spaceflight involving *civilians* and their attendant unique phenotypes. With time, the IRB-C will become the

research ethics board with the most experience involving the space faring general public and how their attendant comorbidities interact with the spaceflight environment.

STATEMENT OF WORK

- Establish the guidance for the IRB-C, based on the US Office for Human Research Protections (OHRP) guidance. In other countries, utilize local guidance.
- Develop policies, procedures, and SOPs for the IRB-C
- Register with the appropriate government agency. In the United States, this is the (OHRP)
- Acquire Institutional Federal-Wide Assurance (FWA) with OHRP (USA)
- Establish the IRB-C leadership and membership

Leadership and Oversight

IRB-C Membership Structure

- IRB-C members should have experience with conducting human research in space with the exception of the one or two lay members.
- Chair: Physician or scientist with IRB experience
- Representatives from commercial flight providers and other commercial entities
- Representatives from NASA and/or FAA
- Bioethicist
- Civilian space traveler or another lay representative (2)

Relationship to other topics

The IRB-C is the center of quality control over all human research. While the HSRB oversees the overall research efforts of the HRP-C and establishes research priorities, the IRB-C is the sole organization dedicated to the review and approval of specific research proposals, projects, and domains, as outlined in Tracks 1 and 2.

5.6 PHYSICIAN CONTINUING EDUCATION

As the human presence in space increases, medical knowledge will expand at an exponential rate. New research, treatment modalities, and diagnostic techniques will emerge transforming the understanding of spaceflight risks, countermeasures, and health management. Continuing education will enable physicians to stay updated with these advancements, ensuring that they can offer the most current, evidence-based care.

The HRP-C will generate significant scientific and medical data, which must be converted into a knowledge base. This knowledge base will then have to be translated into a set of concepts, methods, and practices in a form that can be conveyed to practicing clinicians. This requires that a dedicated curriculum be developed that can be formalized as continuing medical education for the purpose of expanding the clinical pool who can successfully support civilians in space.

As the results of knowledge about physiologic changes during spaceflight evolve, a formalized method of communicating the knowledge to medical providers will ensure dissemination of critical medical information. Currently, some medical clearance is obtained in the American civilian sector through formalized medical exams such as those provided by FAA Aviation Medical Examiners, and physicians who perform Commercial Driver's License (CDL) exams. These formalized medical encounters are performed by physicians who have undertaken additional continuing education and training to act in these specialized roles. Continuous education for physicians specializing in space medicine becomes paramount to anticipate and manage health issues that may arise during extended stays in space. They must grasp the nuances of physiological adaptations in microgravity, understand the implications of individual physiology, and be equipped to mitigate psychological stressors that could impact performance and well-being. Other physicians not directly involved in spaceflight operations will eventually have patients that might be requesting evaluation for a patient's suitability for spaceflight, or for evaluation of a condition that might have developed from spaceflight operations. These physicians will require avenues to obtain clinical pearls and knowledge to care for these patients.

STATEMENT OF WORK

Research communicates its results to practicing physicians through various channels tailored to their needs and preferences. The HSRB-C should have an organizational plan to ensure timely and clear communication of key lessons learned from the research process. Here are some common methods:

- **Medical Journals:** Peer-reviewed journals remain a primary source for disseminating research findings. These publications cover a wide array of medical specialties, presenting original research, reviews, case studies, and clinical trials. Articles are written in a format that allows physicians to access detailed methodologies, results, and implications for clinical practice.

- **Conferences and Symposia:** Medical conferences and symposia provide platforms for researchers to present their findings to a broader audience of healthcare professionals. These events often include sessions where researchers share their work

through presentations, posters, and discussions. This allows for direct interaction between researchers and practicing physicians, fostering dialogue and the exchange of ideas.

- **Continuing Medical Education (CME):** CME programs are designed to educate and update practicing physicians on the latest research and advancements in their field. These programs can take various forms, including live seminars, online courses, webinars, and workshops. They focus on translating research findings into practical knowledge that physicians can apply in their clinical practice.

- **Clinical Practice Guidelines:** Organizations like medical societies or professional associations develop evidence-based guidelines summarizing key research findings and recommendations for clinical practice. These guidelines synthesize complex research outcomes into actionable steps for physicians, offering standardized approaches to diagnosis, treatment, and patient care.

- **Medical Websites and Databases:** Online platforms and databases curate research articles, reviews, and summaries tailored for healthcare professionals. These resources often provide easy access to up-to-date information, allowing physicians to search for specific topics or latest developments relevant to their practice.

- **Direct Outreach and Communication:** Pharmaceutical companies, medical device manufacturers, and research institutions often disseminate research findings directly to healthcare providers through targeted campaigns, newsletters, and sponsored educational events. While these sources can be informative, they may also have commercial interests.

- **Peer Discussions and Collaborations:** Informal networks, multidisciplinary team meetings, and collaborations among healthcare professionals foster discussions about recent research findings. These interactions allow physicians to share insights, experiences, and interpretations of research in a more personalized and interactive manner.

Overall, effective communication of research results to practicing physicians involves a multifaceted approach, recognizing the diversity of preferences and learning styles within the medical community. The aim is to make research findings accessible, relevant, and applicable to clinical practice, ultimately improving patient care outcomes.

5.7 CIVILIAN TRAINING

The HRP-C will highlight gaps in knowledge and generate significant scientific and medical data. The gaps shown will inform research required to decrease risk and improve health outcomes of civilian space travelers. The data generated must be converted into a knowledge base. This knowledge base will have to be translated into a set of concepts, methods, and practices in a form that can be conveyed to civilians preparing to enter the spaceflight environments. While numerous companies have emerged and more will emerge that provide civilian astronaut training, the curricula offered must be evidence based and incorporate the knowledge base developed for clinicians and expanded to serve the needs of civilians. This requires that recognized and standardized curricula be developed that can be tailored to enhance the extant civilian spaceflight training programs and support the evolution of new training programs.

The programs ultimately employed must optimize civilian space traveler performance of routine activities, optimize their ability to react to emergency situations, and enable health to either be maintained at pre-flight levels or at least within acceptable limits. Although civilians on the whole will not be trained first responders, one of the goals of the training provided should be to ensure that the civilian space traveler is able to help stabilize the patient and/or circumstances, and provide appropriate care until more highly skilled crew arrive to take over the treatment.

What is important with respect to the production of the necessary training programs is that the proposed standards are recognized academically, based on current industrial norms, that the programs are certified by an appropriate body, and that all parties (academic, industrial, government) subscribe to the adoption of the agreed standards, to maximize the potential to maintain the health of civilians traveling to/from and spending time in space.

STATEMENT OF WORK

- Establish/modify appropriate policies, procedures, and guidance in consultation with suitable certification bodies e.g. FAA for the US, CAA for Europe, and IRB-C.
- Establish cross party agreement (academic, industrial, government) on the minimal standards to be adopted for space preparation training for each DRM.
- Identify and establish the necessary infrastructure for the training of large numbers of civilians intending to travel to space.

5.8 AI AND PREDICTIVE MODELING

Artificial Intelligence (AI) refers to the development and utilization of computer systems that can perform tasks that typically require human intelligence. AI systems are designed to emulate cognitive functions such as problem-solving, reasoning, perception, and language understanding,

enabling them to execute complex tasks without explicit programming. The field of AI encompasses various subfields, including machine learning, natural language processing, computer vision, and robotics, with the goal of creating intelligent machines capable of autonomous decision-making and problem-solving (though one can argue the value of maintaining humans in the loop).

Within the context of spaceflight research and the HRP-C, Artificial Intelligence (AI) comprises several major components, each contributing to the development and functionality of intelligent systems. The key components of AI include:

- **Machine Learning (ML):** ML is a subset of AI that focuses on enabling machines to learn from data without being explicitly programmed. It includes algorithms and techniques that allow systems to improve their performance on a task over time.
- **Neural Network Analysis:** Neural networks are a fundamental aspect of machine learning and are inspired by the structure and functioning of the human brain. They are used for tasks such as pattern recognition, classification, and regression.
- **Knowledge Representation and Reasoning:** This involves organizing and structuring information in a way that allows AI systems to make informed decisions. It includes methods for representing knowledge and using logical reasoning to draw conclusions.
- **Expert Systems:** Expert systems are AI programs designed to mimic the decision-making abilities of a human expert in a specific domain. They use a knowledge base of human expertise and an inference engine to make decisions or solve problems.
- **Planning and Decision Making:** AI systems need the ability to plan and make decisions based on their understanding of the environment. This involves algorithms and techniques for determining the best course of action to achieve specific goals.

A significant limitation of spaceflight research is the paucity of data towards specific space environment related problems due to the limited number of subjects that have flown in space and the limited data that has been collected on them. Further, proper artificial intelligence application requires large amounts of data in order to accurately train, test, and verify models adequately (in most cases). To deal with this problem of fragmented studies and datasets dealing with the most pressing problems outlined by the spaceflight human research community, a method is needed to aggregate the knowledge of known, germane literature and produce meaningful insight. To that end, the development and application of an astronaut digital twin is an expert system for knowledge representation and reasoning that can be leveraged as one method for clinical and research applications.

Industries such as aerospace and aviation have successfully implemented AI in the form of virtual digital twin models to understand the real-time performance of engineered systems. The

translation of the digital twin paradigm (sometimes called biodigital twins) into biological systems and human medicine has been rapidly advancing into areas such as cardiovascular (Mansi et al., 2020) and cognitive health (Nath & van Schalkwyk, 2021). The core of biodigital twin modeling involves quantitatively representing homeostasis using diverse data sources, including published literature and novel data, to capture population variability. This includes the application of systems of nonlinear differential equations and Bayesian inference (C. Schmidt et al., 2023).

Sources of variation encompass genetic, molecular, physiological, lifestyle-centric, and environmental factors. The deployment and utilization of biodigital twins is two-fold. From a clinical perspective, biodigital twin models streamline the representation of complex physiological interactions, focusing on the relevant subset of an astronaut's physiology for specific objectives (e.g., mitigating issues caused by fluid shifts associated with microgravity). Since modeling the entire human system is of daunting complexity, this is achieved by using constrained network approaches that incorporate a reduced number of inputs having the greatest effect size associated with the desired output.

With an astronaut digital twin, one goal is to enable precise real-time predictions of health status and performance trajectory during missions. Through simulating physiological changes in microgravity and other spaceflight-associated stimuli, biodigital twins can proactively identify potential health risks and performance issues, optimize countermeasures, and generate personalized intervention strategies. Additionally, through a research lens, the astronaut digital twin is expected to better facilitate a unique understanding of novel datasets, uncovering novel mechanisms and patterns for iterative discovery in spaceflight (M. Schmidt et al., 2023). That is to say, the addition of other artificial modalities and capabilities can be easily coupled with the astronaut digital twin platform and will increasingly become an essential component of supporting the success of civilian space travelers.

In summary, the digital twin platform has the ability to provide: 1) detailed assessment of astronaut risk and performance trajectory, 2) “What If” counterfactual analysis to determine response/non-response to numerous countermeasures, and 3) iterative learning from longitudinal data, adapting to changes from countermeasures, and reducing predicted variance in underlying predispositions.

5.9 PRECISION MEDICINE

Precision Medicine (PM) in space is defined as the science and practice of providing methods of treatment and prevention tailored to an *individual’s* molecular, physiological, morphological, and behavioral characteristics. A related requirement is that the assessment and countermeasures

must be aligned to the specific space context in which the individual is operating. Each environment carries unique exposures, risks to injury, or risks to illness to which the countermeasures must also be tailored (M. Schmidt et al., 2016; M. Schmidt et al., 2020; M. M. Schmidt et al., 2023).

It is important to identify two concepts within the application of precision medicine in space: *stratification* and *personalization*. Stratification applies to groups of individuals, whereas personalization applies to a single individual. Both stratification and personalization are foundational to PM in space. Stratification applies when patterns of variance are identified within a group from which a shared suite of countermeasures can be developed. This may apply to crews, teams, units, or other types of small and large groups. Personalization applies when a careful evaluation reveals a unique pattern of variance whereby countermeasures are tailored to one individual.

The term *countermeasure* is used in spaceflight applications because these are methods that are not typically centered on the treatment of disease. While there are several related definitions of the term countermeasure, a useful definition for our purpose is *solutions to prevent the undesirable physiologic outcomes associated with an extreme environment* (Ploutz-Snyder, 2016).

One key distinguishing feature of PM in extreme environments is the requirement for optimal *performance,* which is not inherent to PM in general practice. Optimal performance is defined as the degree to which individuals achieve a desired outcome when completing goal-oriented tasks. By the nature of its difficulty, an extreme environment such as space commonly renders completion of specific tasks much more challenging (Paulus et al., 2009). Therefore, a smaller number of individuals may be capable of optimally performing a given task. In practice, PM must always attend to raising the individual's capability to operate in pursuit of executing such tasks (M. Schmidt et al., 2023).

Performance is not only a requirement for proper execution in space, but it is often tightly linked to operational *safety* and even *survival*. Thus, PM applied to spaceflight must consider incremental factors that can influence endurance, psychomotor speed, cognition, decision making, execution of tasks, response time, mood, team cohesion, and numerous behavioral dynamics. In addition, a foundational premise of operating in space is not only that one thrives in standard (or nominal) conditions, but that one be able to respond to emergencies (off-nominal) with often limited access to emergency services or needed resources.

Humans operating in space have unique needs that are sometimes not fully addressed by traditional medical methods. Moreover, precision medicine applied to humans in space has unique requirements beyond those of precision medicine in general practice. As summarized by

Schmidt et al, among the goals of precision medicine in space are to 1) identify individual deficits in essential and conditionally essential nutrients, 2) identify elements of the exposome with health and performance implications, 3) optimize metabolic networks, 4) personalize drug therapeutics to improve safety and efficacy (especially to minimize drug-associated adverse events), 5) improve diagnostic accuracy, 6) reduce unnecessary variations in diagnosis, 7) improve predictive ability regarding outcomes, 8) personalize preventive measures, countermeasures, and therapies, 9) improve performance, 10) improve recovery from training, operations, and injury; 11) better match countermeasures with the operating environment (DRM); 12) improve astronaut decision making; 13) improve crew cohesion; 14) provide direction on intervention in cases where research is limited; 15) optimize career longevity; and 16) optimize health upon retirement. This approach will be particularly important to civilians in space, because many will present with comorbidities, deficits in conditioning, complex medical therapeutics (e.g., polypharmacy), implanted medical devices, and a range of variants uncommon in professional astronauts, which warrant precise individualization (M. Schmidt et al, 2023).

Point 14 warrants specific attention. There is presently little data on civilians traveling, living, and working in space. With this paucity of data, it will be of particular value that comprehensive analytics and personalized intervention be applied to spacefaring civilians. This approach will provide incremental gains in the efficiency of the molecular, physiologic, behavioral, and morphologic phenotype of each astronaut.

STATEMENT OF WORK

- Establish the primary infrastructure conditions needed for a precision medicine program
- Establish the primary operational considerations needed for a precision medicine program
- Identify entities that currently operate civilian spaceflight precision medicine programs, as potential candidates for the HRP-C precision medicine program

5.10 SPACEFLIGHT COUNTERMEASURE DEVELOPMENT

The variable gravity, radiation, and isolation conditions of spaceflight induce multiple changes to both human anatomy and human physiology. These changes range from creating a new normal within the microgravity environment to potential pathological conditions, inconsistent with good health. Moreover, some of the benign changes that do occur in spaceflight may be harmful to the individual either immediately on return to Earth or sometime during their lifetime. Some or all these problems have been identified for the career astronaut population and appropriate countermeasures are being used or developed. Whereas professional astronauts could be

thought to be within the top 2% of healthy individuals, commercial spaceflight will be less restrictive on who is allowed to visit, work, and live in low Earth orbit or in the future, possibly the Moon or Mars.

The direct health consequences of spaceflight can either be symptomatic (physiologic) or structural based on the organ system affected. The indirect health consequences can be due to the underlying health of the civilian space traveler.

The spaceflight countermeasures program is a dedicated effort to assemble and analyze the emergent data from the HRP-C and use a systematic effort of lead optimization to prioritize (and pursue) the development of countermeasures specific to addressing these health consequences. It is important to note that many countermeasure efforts are left to emerge organically out of research projects and are largely driven by investigators and their institutions. The HRP-C effort will be funded and formalized, so that there is a continual and sustainable countermeasure effort housed within the HRP-C framework.

Countermeasures can be viewed from the vantage point of the specific solutions that will be pursued and developed for civilians in space. Alternately, countermeasures can be viewed from the perspective of the types of problems that need to be solved (and for which specific countermeasures need to be developed). For the purpose of the HRP-C dossier herein, we have chosen to outline selected types of problems that persist and need to be solved for civilians in space. By extension, one can then assume that a dedicated countermeasure development effort is needed in order to address each of the specific problems being described, as is done below.

Examples of symptomatic effects of spaceflight launch, inflight and landing symptoms that are known to affect most professionally astronauts to a limited degree include space motion sickness, headaches, backaches, and changes in visual perception during spaceflight and orthostatic intolerances or motion sickness (feeling lightheaded or dizzy) on initially returning to Earth. More serious

Examples of structural effects caused by spaceflight microgravity include lower body muscle and bone atrophy, decrease in total vascular and extravascular fluids and, also, redistribution of these fluids into the upper body. reshaping of the spine and heart, and changes in the body's reflexes. The potential of increasing lifelong cancer risk from increased radiation absorption during spaceflight.

Examples of indirect health consequences in the general population during a space mission include exacerbation of kidney stones (due to increased bone turnover), inability to urinate (due to changes in bladder and urethra reflexes), and exacerbations of cardiac arrhythmias (stress associated with launch and landing or spaceflight)

Like the use of preventative measures to protect health on Earth, preventative measures will be needed for civilian space travelers to prevent or modify microgravity or partial gravity induced physiologic changes and to reduce risk from health conditions spaceflight participants are already known to have. Possible countermeasures will have to be determined for individuals not only to make their spaceflight more comfortable but to protect their health.

Impact

The ultimate goal of the HRP-C is to develop solutions for humans to thrive in space. Thus, all research is conducted with the fundamental guiding principle that countermeasure development is at its core. These countermeasures can take many forms that include but are not limited to 1) spacecraft or habitat engineering for better human systems integration, 2) tools of clinical assessment, 3) non-invasive sensors and monitors, 4) therapeutic or prophylactic food, nutrients, drugs, or other ingestibles, 5) medical devices, 6) surgical tools, 7) remote/emergency medicine tools and techniques, and 8) others.

It is important to further note that the HRP-C countermeasure effort will feed directly into the Terrestrial Applications Program. This will create a continuity from 1) spaceflight research to, 2) space-directed countermeasure development, to 3) terrestrial countermeasure development for clinical medicine on Earth. A substantial social benefit to humanity is expected to emerge via the formal manner in which the monies spent on civilian space research will return to Earth.

5.11 TERRESTRIAL APPLICATIONS PROGRAM FOR CIVILIANS (TAP-C)

There is a long history of spaceflight operations generating novel inventions that translate into new technologies that become useful, if not revolutionary, on Earth. Government space programs have already returned advances to the terrestrial economy in materials, power generation and storage, recycling and waste management, advanced medical robotics, remote biomonitoring, bioanalyzers, smart materials, smart clothing, g-suit technology to prevent postpartum hemorrhage, telemedicine, point-of-care diagnostics, healthy aging applications, 3-dimensional tissue models for cancer discovery and regenerative medicine, surgery, water purification, air purification, other health and medicine applications, transportation, engineering, computing miniaturization, software, artificial intelligence, and many others (Shirah et al., 2023; Grimm et al., 2022; Shelhamer et al., 2020).

The HRP-C is expected to generate considerable amounts of data from civilian spaceflight missions. While investigators are often driven to explore and articulate the clinical ramifications of their research findings, this generally does not proceed as a consistent or coordinated effort. The Terrestrial Applications Program for Civilians is a dedicated effort focused on translating

medical procedures, methods, and technology into practical Earth applications that have a benefit to society as a whole. This will differ from the Countermeasures Program, since the countermeasures group is focused on the identification and development of novel methods and technologies that will specifically serve the clinical methods and practices *in space*.

There are numerous ways in which research on civilians in space can benefit civilians on Earth. For example, many of the common medical conditions seen during human spaceflight, such as motion sickness, osteoporosis, and sarcopenia are also experienced by humans on Earth. As such, research on these and other spaceflight-associated medical conditions will likely lead to improvements in the treatment of many diseases on Earth. However, the benefits of research on civilians in space go far beyond the treatment of any specific disease. It offers the opportunity to look at the system as a whole.

The unique stressors encountered by civilians as they work and live in a spaceflight environment over longer periods of time, and the lack of immediate hospital resources, will require a more proactive and holistic approach to human health and disease. Such an individualized, yet contextualized, approach could benefit civilians on Earth in the following ways: incorporating precision medicine into primary care, improving the resilience of civilian communities, improving the coordination of healthcare service delivery, and providing a framework for quality improvement programs using systems-based risk mitigation strategies.

Providing individualized, contextual care through the use of untargeted multiomics is the essence of precision medicine and molecular phenotyping described earlier as part of the HRP-C. Precision medicine allows for the modeling of individuals as complex adaptive biological systems. In particular, understanding the effects of environmental exposures, such as air pollution, biological pathogens, or psychological trauma, on genetic expression and emergent physiological and behavioral phenotypes will allow for the development of individualized disease prevention and mitigation strategies for civilians on Earth that were heretofore unavailable.

Such technology could be embedded into the clinical workflows of a new primary care model so all civilians on Earth will have equal access to these new prevention and mitigation strategies. Such strategies do not negate the need for disease management and treatment, they would complement them. For civilians with unmitigated chronic diseases, precision medicine could also improve the effectiveness of prescription medications through pharmacogenomics and similar multiomic strategies. Likewise, in the event of an acute injury or illness, rehabilitation protocols can be customized to an individual patient with their unique functional goals and aspirations.

Beyond improving the care of individual civilians through precision medicine, however, research on the interaction between civilians in space, and the interaction between civilians and their spaceflight environment, will also lead to a greater understanding of humans and technology as complex biosociotechnical ecosystems. Taking a similar systems approach to civilians on Earth

with their network of available resources (or lack of resources) allows for the integration of non-medical interventions, such as housing, transportation, employment, government services, etc. into the care of individual patients. Developing models that integrate these "social" determinants of health with "molecular" determinants of health allows for a more complete modeling of individuals and the communities in which they live. Such models could lead to novel interventions that improve community resilience and reduce the incidence of acute medical events that lead to costly, and otherwise unnecessary, hospitalizations.

Furthermore, research that considers the coordination of medical care to civilians in space with a network of medical providers on Earth could improve the overall efficiency of care delivered to civilians in space. While missions of greater distance from Earth will impose significant time-delays in communication, most medical care in space for the foreseeable future will allow for communications with, if not evacuations to, a higher level of care on Earth. Such emergency evacuations, however, will be extremely costly, and an excessive number of evacuations could potentially jeopardize the financial viability of any company with a civilian space program.

In order to mitigate the financial risk of providing medical care to civilians in space, the entirety of the care continuum from prevention to chronic disease management to acute care services to rehabilitation services will need to be coordinated between primary care, specialty care, hospital care and rehabilitation care to promote the most effective and efficient use of medical resources. Such care coordination protocols would add enormous value to healthcare delivery on Earth by minimizing the need for unnecessary and expensive specialty care and hospital resources.

Finally, knowledge transfer from civilian spaceflight to terrestrial medicine will need to be incorporated into existing healthcare quality improvement programs for successful implementation. However, extant quality improvement programs are often disconnected from the research community. Furthermore, most programs drive behaviors that affect only single quality measures and do not consider the system as a whole. The HSRB-C component of the HRP-C will be designed to provide a "standardized, rigorous, and transparent mechanism for identifying, categorizing, and prioritizing risks" in civilian spaceflight. Such mechanisms could also be utilized to develop systems-based continuous risk mitigation strategies in terrestrial-based healthcare systems.

With its focus on individualized, contextual care in a resource-constrained environment, research on civilians in space can help develop a new paradigm for healthcare delivery on Earth. Such a paradigm can incorporate precision medicine into primary care to develop individualized disease prevention and mitigation strategies; maximize the resilience of civilian communities; improve the coordination of medical care for more efficient use of medical resources; and help develop new quality improvement programs based on continuous risk mitigation strategies. With an HRP-

C in place, civilian spaceflight could serve as a small-scale laboratory for the advancement of terrestrial-based medicine.

STATEMENT OF WORK

- Establish the guidance for the TAP-C
- Develop policies, procedures, and SOPs for the TAP-C
- Establish the TAP-C leadership

5.12 PREPARATION AND CONTINGENCIES

Emergency medical preparation and contingency planning in the context of space travel involves meticulous strategies to address unforeseen medical emergencies in the unique and challenging environment of space. Spacefaring civilians will encounter an amalgamation of stressors, from the confines of enclosed habitats to prolonged separation from Earth and loved ones. Given the isolation, limited resources, and potential risks associated with space missions, preparing for medical contingencies is paramount to ensure the health and safety of astronauts or spacefaring civilians.

Preparation entails familiarization with expected environmental conditions and comprehensive training, not just in technical skills but also in mental resilience and adaptability. Civilians bound for space should undergo rigorous simulations and training exercises that mirror the complexities of space environments. This training should encompass emergency response protocols, equipment handling, EVA (extravehicular activity) procedures, operational processes, and techniques such as how to exercise in microgravity, and strategies to manage high cognitive workloads and physical exertion in challenging conditions.

Contingencies in space missions require meticulous planning for potential medical emergencies, equipment malfunctions, and psychological distress among crew members. A robust contingency plan involves redundancies in critical systems, access to medical supplies, and the ability to address unforeseen challenges autonomously. Contingency planning should include awareness of the potential for participants with disabilities and how that will affect their ability to respond or react during an emergency. Models and best practices should ideally be freely shared by the HSRB-C.

5.12.1 Training and Simulation

Medical Training: Astronauts and designated medical crew members undergo extensive medical training to handle emergencies. This includes basic life support, advanced cardiac life support,

trauma management, and other specific skills relevant to space. Consideration of training spaceflight participants in a first-aid level of knowledge about microgravity medical changes and injury could be beneficial. This may include certification courses common in wilderness medicine operating space, which can be tailored to the space environment.

Simulation Exercises: Simulated emergency scenarios are conducted in space analog environments or specialized facilities to replicate the challenges of medical emergencies in space. These exercises help astronauts practice responses and familiarize themselves with medical equipment in a microgravity setting.

5.12.2 Medical Equipment and Supplies

Medical Kits: Specialized medical kits containing essential drugs, equipment for airway management, cardiac monitoring, defibrillation, wound care, and medication for common ailments are carried onboard spacecraft or space stations.

Telemedicine Support: Establishing telemedicine capabilities allows communications with medical experts on Earth for guidance in managing complex medical situations.

5.12.3 Remote Medical Guidance

Ground Support Teams: A team of medical professionals on Earth provides real-time guidance to astronauts during medical emergencies, aiding in decision-making and providing step-by-step instructions for medical procedures. Industry analogs will be beneficial in extended and remote spaceflight operations. Consultancy operations currently existing in the aviation industry can serve as a model for the commercial space industry.

5.12.4 Redundancies and Backup Systems

Redundant Systems: Backup medical equipment and redundant systems are in place to ensure that critical medical devices remain operational in case of equipment failure.
Emergency Protocols: Clearly defined emergency protocols and procedures are established, outlining step-by-step actions to be taken during various medical emergencies, ensuring a systematic response.

5.12.5 Psychological Preparedness

Psychological Support: Training includes preparing spaceflight participants to handle the psychological stress of medical emergencies, addressing the potential impact on mental health, and fostering resilience in challenging situations.

5.12.6 Collaboration and Resources

Collaboration with Medical Experts: Collaboration with medical experts, both within and outside of the space industry, allows for continuous learning, sharing of best practices, and updating protocols based on the latest medical advancements.
Research and Development: Ongoing research and development in medical technology aim to improve medical equipment, treatment modalities, and emergency response strategies for space missions.

5.12.7 Continual Evaluation and Improvement

Post-Mission Analysis: After each mission, a thorough analysis of medical incidents and responses helps refine emergency protocols and identify areas for improvement in medical preparedness for future missions.

Medical providers and spaceflight operators should continually refine and enhance emergency medical preparation and contingency planning to ensure that astronauts or civilian space travelers have the necessary resources, skills, and support systems to address medical emergencies effectively, promoting the safety and success of space missions.

Furthermore, fostering a culture of continuous learning and adaptability among spacefaring civilians is paramount. The ability to troubleshoot, improvise, and collaborate effectively in the face of unforeseen circumstances is as crucial as following established protocols. By integrating preparation and contingencies seamlessly into the fabric of space missions, the resilience and success of civilian endeavors in space can be ensured.

5.13 FOOD, NUTRITION, AND METABOLISM

Diet and nutrition are among the most influential factors affecting human health, safety, and performance in space. NASA has provided a safe food system for astronauts on four- to eleven-month missions on the ISS. However, there is limited crew time, food preparation capability (e.g., adding water or heat), water, and storage. These limitations constrain the crew to a small number of single-serving, shelf-stable food products that are either preserved (e.g., by dehydration, thermostabilization, retort, radiation) or in their natural form. Roughly 80% of the astronaut diet

comes from a standard set of foods that are shared, leaving the remaining 20% for self-selection (Douglas et al., 2020).

In order to optimize food intake and more carefully study the effects of food intake in astronauts (micronutrients and macronutrients), NASA has implemented the food intake tracker (NASA FIT). Using FIT also as a monitor of energy intake, astronauts are encouraged to increase food consumption (when indicated) in order to meet the objective of maintaining their body mass at preflight levels (Smith et al., 2021). Similar monitoring solutions will be important for civilian space travelers.

Also important will be a careful assessment of nutritional status during training and preparation before entering the space environment, using the tools of molecular analytics. This will provide quantitative guidance to ensure that knowable, actionable nutritional deficits are not carried into the space environment where the space exposure may further deplete an already nutritionally depleted civilian space traveler (M. Schmidt et al., 2023).

Related pre-mission biochemical measures will also become important. For example, circulating biomarkers of both bone resorption (urinary N-telopeptide (NTx) and C-telopeptide) and bone formation (serum procollagen 1 intact N-terminal propeptide) before spaceflight predicted changes in bone turnover in space (Gabel et al., 2022). Such biochemical analyses may one day form the basis for precision medicine applications, allowing us to better understand who is at greater risk of bone loss in space and what types of countermeasures are most appropriate for individuals.

Diet and nutrition are among the most influential factors affecting human health, safety, and performance in space. The value of attention to nutrition can be illustrated by a recent NASA HERA study. NASA uses the Human Exploration Research Analog (HERA) in Houston to study controlled habitation on Earth as an analog for spaceflight. The *HERA Campaign 4* encompassed a 45-day mission examining the effect of a standard spaceflight diet (common on the ISS) and compared it with an enhanced diet (ED) in 16 participants.
.
The enhanced diet provided > 6 servings fruits and vegetables per day, 2-3 servings (8-12 oz) of fish per week, > 5 tomato-based (lycopene-rich foods) per week, and >2 flavonoid-rich foods per day. Protein intake was maintained between 1.2 and 1.7 g/kg/day, vitamin D at 800 IU/day, iron around 10 mg/day, calcium between 1,000 and 1,200 mg/day, and sodium around 2,300 mg/day.

Among numerous measures, investigators evaluated vigilant attention using the Psychomotor Vigilance Test (PVT), which was administered twice at baseline (pre-mission) and three times

weekly over the 45-day mission. Those on the enhanced diet showed improved reaction speed ($p = 0.014$), improved accuracy ($p = 0.022$), and fewer attention lapses ($p = 0.0047$) than those consuming the standard diet during the mission (Douglas et al., 2022). While PVT is not a direct measure of performance, it has been shown to be predictive of simulated spacecraft docking performance (Basner et al., 2020) and is correlated with rates of serious medical errors made by resident physicians (Rahman et al., 2021). In general, this study demonstrated the potential impact of a basic dietary enhancement on an important measure associated with success in a space analog environment.

There are fundamental questions that warrant attention for the development of an optimal food and nutrition program for civilians in space. These include (but are not limited to):

- What is the nutritional status of each civilian who prepares to enter the space environment? This is generally determined via clinical laboratory assessment.
- What are the optimal means to correct such deficits? Food? Supplementation?
- What is the general foundational diet needed to prepare individuals to fly into and inhabit space?
- Beyond the foundational diet, what are unique dietary needs for a given individual?
- How do we best meet the requirements of those with special dietary needs in space?
- How will these individual needs be met: via food or via supplementation?
- Are there specific genotypes that alter the nutrient demands of individuals? This may also (if sufficient informed consent is given and civilian space travelers give consent) benefit from individual genotyping to assess for genetic variants that may increase or alter the need for different nutrients. These include genes such as FADS1, MTHFR (including MTR, MTRR, SHMT1, PEMT, etc.), HFE, and others.

Despite considerable advances, there remains a series of limitations regarding existing space nutrition, which scales with mission distance and duration. These include, but are not limited to (Tang et al., 2021):

- Dominance of Processed over Fresh Food
- No Quality Advantage for Resource-Intensive Refrigerated and Frozen Food
- Space Food Supply is Restricted by Limited Transportation and Storage Space
- Long-Term Space Nutrition Requirements for Food Storage and Cooking Methods
- Diet Menu Fatigue, Food Acceptability
- Lack of Nutrients to Cope with Extreme Conditions of Space
- The Influence of Adverse Space Environment on Astronauts' Diet and Health
- Less Energy Intake and Weight Loss

- Effect of Microgravity on Fluid redistribution, loss of muscle mass, deconditioning, etc.
- Long-Term Radiation and need for protective nutrients
- Nutrient depletion such as iron, zinc, and magnesium
- Fluid and electrolyte imbalance
- Altered digestion and absorption

Statement of Work

- Evaluate the state of the field in astronaut nutritional status assessment
- Evaluate the state of the field in space food and nutrition product development
- Identify gaps in each of the above
- Prioritize the food and nutritional needs of civilian space travelers today
- Balance the needs for food vs dietary supplements
- Prioritize areas of food and nutrition in need of further immediate support

6.0 DESIGN REFERENCE MISSION (DRM) AND THE SPACE ENVIRONMENT SUMMARIES

Design Reference Missions (DRM) are a way of categorizing the space environments present for different mission profiles ranging from sub-orbital to interplanetary flights. Not only do the DRMs serve to inform mission operations, but they also have a significant impact on the types of research and the data collected that will yield the information required for evaluating how civilian space travelers might fare in the various mission environments.

For the HRP-C objective, seven classes of DRMs were defined. These definitions are based on mission altitude/distance from the Earth and mission duration because the environment that will be experienced by the crew is a function of where they are and how long they are there. This is particularly important when considering the effects of micro- or reduced gravity and radiation on the human body. The DRM classes are:

- Suborbital, including point-to-point suborbital transportation
- Low Earth Orbit (LEO)
- Medium Earth Orbit (MEO) to High Earth Orbit (HEO)
- Geosynchronous and Geostationary Orbits (GEO)
- Cislunar Space (transit, lunar orbit, surface operations)
- Mars (transit, Mars orbit, surface operations)
- Beyond Mars, e.g., the Main Asteroid Belt (MAB)

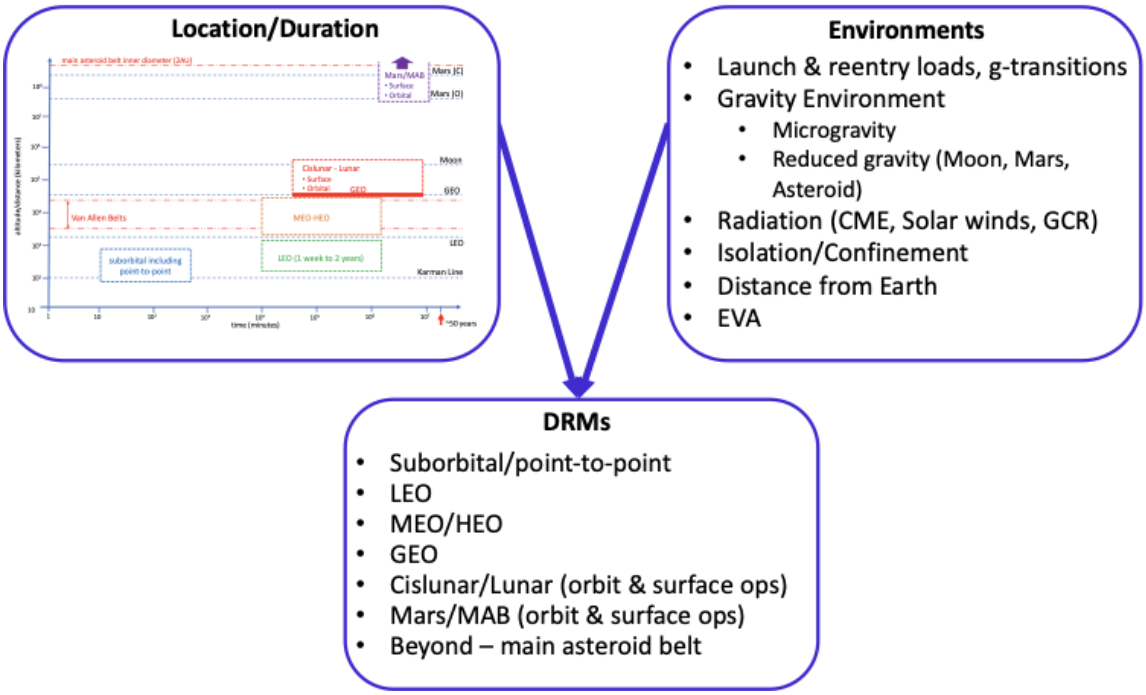


Figure 6 Mission Locations, Durations, and Expected Environments Factored into DRM Definitions

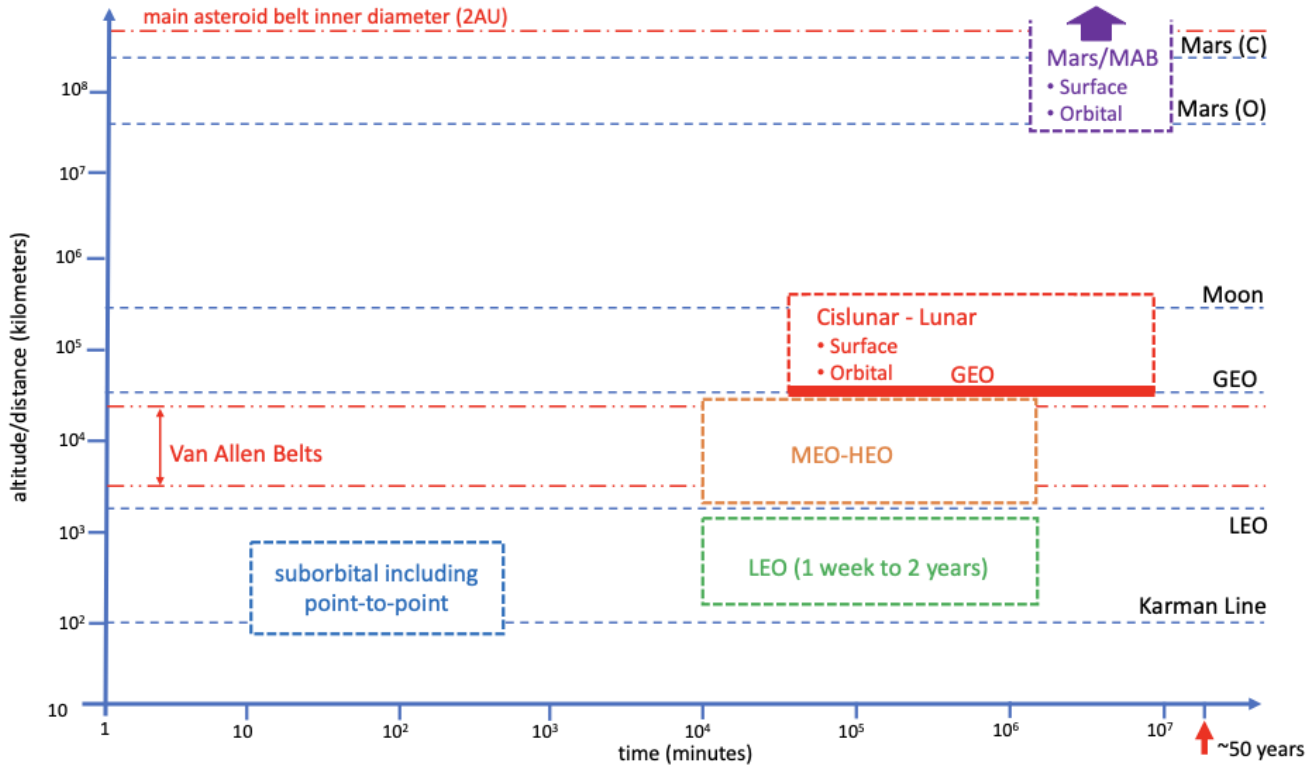


Figure 7 Graphic Depiction of The Range of Locations and Durations of the Seven Design Reference Mission Classes Note the logarithmic scales. Distances and times are approximately to scale.

6.1 DESIGN REFERENCE MISSION LOCATION & DURATION DESCRIPTIONS

6.1.1 Suborbital. The first class of missions addresses crewed suborbital flights. These flights last from just a few minutes up to several hours, when including point-to-point suborbital transportation flights. The mission altitudes will vary from slightly less than 100 km up to approximately 1000 km, depending on the suborbital trajectory. The mission durations range from just over 10 minutes potentially up to several hours. Therefore, the time spent in microgravity is short as is the exposure time to a slightly higher level of radiation than would be expected on a long-distance high altitude trans-polar aircraft flight. Flight participants will be exposed to both launch and re-entry high-g loads, ranging from 3 to 5 g. They will also experience two g-transitions including from normal/launch gravity to microgravity and back.

6.1.2 Low Earth Orbit (LEO). Crew members have been surviving, living, and working in LEO since the 1960's. The International Space Station has been occupied for the last 23 years. However, most human LEO missions have been below 500 km, with the longest duration mission by a single individual being 437 days, or a little over 14 and a half months. The LEO DRM for the purposes of

this study is defined as orbital altitudes up to 2000 km with duration from days to up to two years. This period was chosen based on what might reasonably be expected for an on-orbit commercial activity deployment. Missions executed at higher altitudes in the LEO regime will expose the crew to higher radiation levels, though they will still be protected by the Van Allen belts. The Van Allen belts are regions in the magnetosphere in which high energy particles are stably trapped. Crew members will be exposed to launch and re-entry high-g loads and experience two g-transitions similar to the suborbital regime. Depending on the length of the mission and the design of the vehicles, isolation and confinement issues may manifest.

6.1.3 Medium Earth Orbit (MEO) to High Earth Orbit (HEO). While it is not expected that there will be crewed missions launched to MEO or HEO in the near term, the decision was taken to include this mission class in case such missions are eventually planned and executed. The altitudes for MEO span 10,000 to 25,000 km. Altitudes for High Earth Orbit would range between 25,000 km up to near GEO, which is approximately 36,000 km altitude. For the purposes of this study, the mission durations were defined to be from one week up to two years. The microgravity environment for this class of DRM is the same as for LEO. However, many MEO orbits pass through the Van Allen belts exposing the crew and vehicle to higher levels of radiation. The inner Van Allen belt is centered around approximately 3000 km and contains primarily protons. The outer Van Allen belt is centered around approximately 15,000 km and comprises mostly electrons. The belts fluctuate as a function of solar activity.

The average radiation dose rate in the Van Allen belts is approximately 50 Gray/year. Missions that travel beyond the MEO/HEO regime, e.g., to GEO, the Moon or to Mars, must fly through this area of high radiation. Data from the Apollo missions, which flew through the Van Allen belts, indicated a total exposure of 0.02 Gray over six days. Crew members will be exposed to launch and re-entry high-g loads and experience two g-transitions similar to the suborbital regime. Depending on the length of the mission and the design of the vehicles, isolation and confinement issues may manifest.

6.1.4 Geosynchronous and Geostationary Orbit (GEO). The GEO class of DRM is defined separately because of the uniqueness of this orbit. The orbital altitude is 35,786 km with an orbital period of approximately 24 hours. (The actual period is the length of a sidereal day, which is 3.9 minutes less than a solar day.) A spacecraft in GEO orbits the Earth at the same rate that the Earth is turning. For a spacecraft in geostationary orbit, which is an inclination of zero degrees or above the equator, the spacecraft appears stationary from any point on the Earth. This is the reason that satellite television dishes can be aligned once and need not perform any tracking function. For non-zero inclinations, the orbital path traces an analema pattern on the Earth's surface.

Crewed missions to GEO are not expected in the near term. However, they should not be ruled out for future orbital activities given that the GEO orbit is also becoming quite crowded. Crew members will be exposed to launch and re-entry high-g loads and experience two g-transitions similar to the suborbital regime. Depending on the length of the mission and the design of the vehicles, isolation and confinement issues may manifest.

6.1.5 Cislunar and Lunar. The definition of cislunar space varies across agencies and organizations. In general, it is considered to be the space between GEO and just beyond the Earth-Moon Lagrange point 2 (L2). This is a vast amount of volume. The distance to the Moon is 384,400 km, with the distance to L2 being approximately 446,000 km. For the purposes of this study, cislunar space is defined as that volume of space beyond 36,000 km out to 550,000 km. (The resulting volume for this definition is approximately 6.97 x 10^{17} cubic kilometers.) Missions to the Moon and to lunar orbit are planned beginning in the late 2020's. The US plans to develop and launch the Gateway lunar orbiting laboratory, which will be crewed part-time. Missions to the lunar surface are also planned by both the US and China, which will include extravehicular activities (EVAs).

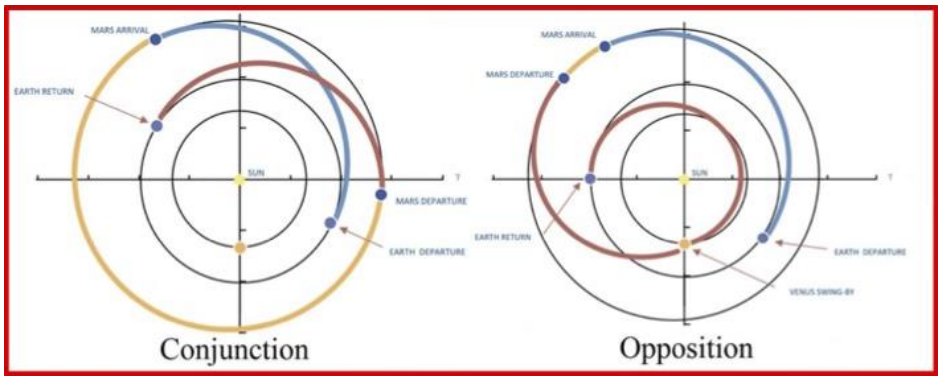
Therefore, when considering this DRM class, lunar orbit, lunar surface operations, and halo orbits around LaGrange points must be considered. As with the other DRMs described above, the orbital environments will impose microgravity conditions and high radiation levels. Lunar surface operations will be conducted in 0.16 g conditions. Therefore, crewmembers will be exposed to four g-level transitions: Earth gravity to microgravity; microgravity to Moon gravity; Moon gravity to microgravity; and microgravity to Earth gravity. Other hazardous considerations, such as dust contamination, must also be considered. Vehicle and habitat design will factor greatly into isolation and confinement issues.

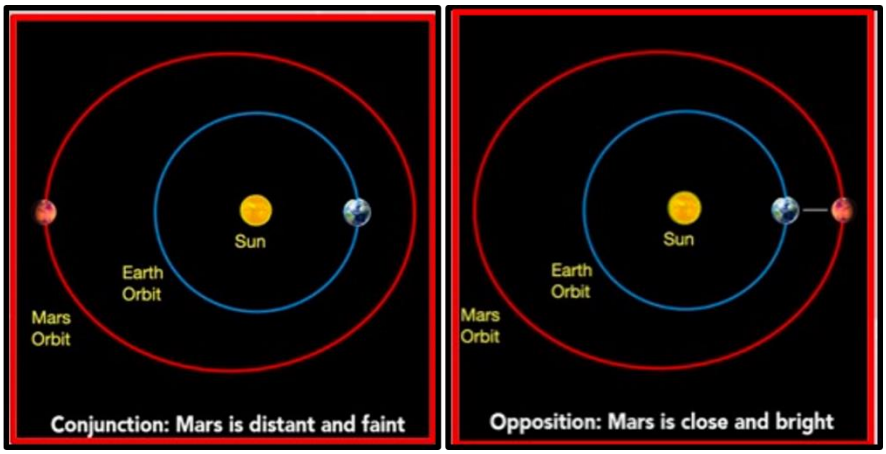
6.1.6 Mars. Crewed missions to Mars are foreseen in the coming decades. Sending explorers on such long excursions will require a significant advancement in the understanding of how long-term exposure to microgravity, confinement, and increased radiation levels will affect humans. The average distance between the Earth and Mars is approximately 225,000,000 km. Because of the way orbital mechanics works, the most energy efficient trajectories are realized missions launched when Mars and Earth are at opposition (Mars is closest to and behind the Earth relative to the Sun) or at conjunction (Mars is farthest from the Earth and behind the Sun relative to the Earth).

Mars' distance from the Earth varies from approximately 56 to 400 million km when at opposition and conjunction, respectively. From either distance, the Earth will appear to the civilian space travelers as a tiny blue dot, which will impact feelings of isolation. Space vehicle and habitat designs must be such that the feeling of confinement is minimized as much as practicable.

Until the development of a highly efficient high-thrust propulsion system happens, trips to Mars will vary from approximately 560 days for opposition class missions to approximately 1005 days for conjunction class missions. This means that Mars crewmembers will experience from approximately 395 to 520 days in microgravity and from 40 to nearly 560 days living and working in 0.38 g conditions. There is no data to indicate how humans will tolerate these conditions. As is the case for lunar surface missions, crewmembers will be exposed to four g-level transitions: Earth gravity to microgravity; microgravity to Mars gravity; Mars gravity to microgravity; and microgravity to Earth gravity. There will also be the ever-present higher levels of radiation as well as the challenges associated with surface operations and EVAs.

6.1.7 Beyond Mars, Main Asteroid Belt (MAB). There are currently no crewed missions planned for going beyond Mars or to the Main Asteroid Belt (MAB). However, for completeness, this DRM has been included. The inner diameter of the MAB is about 300 million km in distance from the Earth. Deep space environments similar to the Mars DRMs are expected with longer terms of exposure to microgravity, radiation, and much reduced gravity levels, should humans conduct surface operations on asteroids. Isolation and confinement issues will be next-level meaning that vehicles and habitats must be designed accordingly.





Mission type [1]	Total mission duration, days	Earth-Mars trip, days	Time spent at destination	Mars-Earth trip, days
Conjuction	1005	198	558	197
Opposition	560	177	40	342

Figure 8. Mars Mission Classes: Conjunction and Opposition.

6.1.8 DRM Environments Summary. NASA has defined a set of DRM categories that are similar to the ones included in this study. The table below summarizes the environments for the DRM categories, which can be mapped to the DRM classes defined above. The table includes mission duration, gravity environment, radiation environment, vehicle and habitat design, distance from Earth, communication delays, and expected EVA frequencies. What is not included are the g-transitions. For missions executed only in microgravity, the two major transitions include going from the high-g launch environment to microgravity and from microgravity to high-g reentry conditions and finally back to 1 g. For surface operations on both the Moon and Mars, there will be four transitions including those just described plus transitioning from microgravity to Moon/Mars gravity and from Moon/Mars gravity to microgravity.

Table 9. DRM Environments. Source: NASA

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

APPENDICES

APPENDIX A

DAG Definitions and Terminology

It is important to understand the definitions and terminology used by NASA. These are reviewed in this section and are formally defined for the agency in the Human System Risk Management Plan JSC-66705. The Human System Risk Board (HSRB) employed a Directed Acyclic Graph (DAG) visual tool that was used to capture knowledge and enhance communication across all the stakeholders of human system risks. The knowledge captured is the Human Health and Performance community's knowledge about the causal flow of a human system risk. They are intended as a high-level resource for understanding the complex relationships between factors that contribute to increased risk within and across the Human Spaceflight System Risks. They are not intended to provide detailed insight into subject matter expert (SME) domains of deep knowledge, but rather to provide the high-level scaffolding to which SMEs can attach more detailed visuals to clearly relay their importance to Mission Level Outcomes.

Hazards are unchangeable aspects of spaceflight that are harmful to humans. The set of Hazards = {Altered Gravity, Radiation, Isolation and Confinement, Hostile Closed Environment, Distance from Earth}.

Mission Level Outcomes are those health and performance outcomes that matter at an agency level as defined by the HMTA. The set of Mission Level Outcomes = {Task Performance, Evacuation, Loss of Mission Objectives, Loss of Crew Life, Loss of Crew, Loss of Mission, Flight Recertification, Long Term Health Outcomes}. A brief description of each of the Mission Level Outcomes of importance to the NASA HMTA are as follows:

- **Task Performance** – impacts to crewmembers' ability to accomplish the tasks they are to perform manifest as risk to in-mission timelines and resources. In the worst case these deficits can lead to loss of mission objectives. To be eligible for consideration for inclusion in a DAG, decrements in Task Performance must be both plausible and measurable.

- **Evacuation** – injury or illness that rises to a sufficiently concerning level may result in consideration of evacuation of the crew from the mission to preserve 'life and limb'. Changing return times to Earth for different DRMs affects the resources required for successful evacuation. In Mars missions, evacuation is not available due to orbital mechanics, so any issues that rise to this level will either self-resolve or lead to death or permanent impairment.

- **Loss of Mission Objectives** – Mission Objectives include the agency purpose for sending astronauts on a given mission. Inability to accomplish these represents the loss of a significant reason for the mission and is high risk for the agency.

- **Loss of Crew Life** – Loss of an individual crew life is a possibility in the human health and performance domain due to injury or illness and represents a Mission Level risk Outcome.

- **Loss of Crew** – Loss of the entire crew, as opposed to a single individual, is typically calculated at the mission safety level separate from health and performance risk calculations. However, there may be cases where Loss of Crew could happen for health and medical reasons.

- **Loss of Mission** – Loss of Mission can result from loss of sufficient mission objectives or loss of crew and is dependent on agency assessment of goals. An example of this is the Apollo 13 mission, where the crew experienced Loss of Mission when they were unable to land on the Moon, but they did not experience Loss of Crew, as they safely returned to Earth. In contrast, the loss of the Space Shuttle Challenger is an example of both Loss of Crew and Loss of Mission.

- **Flight Recertification of Astronauts** – NASA investments in astronaut training and skill sets are critical to mission success. When astronauts experience medical issues incurred from flight exposures, they may be unable medically to recertify for flight.

• **Long Term Health (LTH) Outcomes** – Spaceflight exposures that lead to post-mission medical conditions affect the long-term health and quality of life of astronauts. The Chief Health and Medical Officer at NASA also carries some responsibility for this risk. A common example is the risk of developing cancer from radiation exposures.

Other Key Terms include *Design Reference Missions* (DRM) categories, *contributing factors* and *countermeasures*. These are commonly used in the human spaceflight community to describe what missions we are talking about and what assumptions we make (DRMs), where risk comes from (contributing factors) and what we do to try to mitigate it (countermeasures). Note that some of the countermeasures we use to reduce risk in one area can cause increased risk in other areas. Think about the side effects of medications for example – a medicine that helps reduce space motion sickness can also cause drowsiness at a time when a crew member is expected to perform a complex operation. Recognizing this, in the context of DAGs, all countermeasures are also categorized as contributing factors.

• **Design Reference Mission categories** - NASA mission categories, derived from a subset of risk drivers, loosely defined by destination, operating environment, and expected duration. 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. There are currently four DRMs which are divided into long and short durations.

• **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.

• **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:

o 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, Environmental Monitoring Capability and Inflight Hearing Exams are monitoring countermeasures for the Acoustics Risk. Environmental Monitoring Capability here includes noise monitoring and atmospheric pressure monitoring.

o Prevention Countermeasure – a countermeasure implemented pre-flight and during flight that decreases the influence of contributing factors and hazards on the Risk or on the scenario that enables the Risk to manifest. For example, Environmental Control is a prevention countermeasure for the Acoustics Risk. Environmental Control here includes control over noise levels and atmospheric pressure.

o Intervention Countermeasure – a countermeasure applied after the risk scenario occurs intended to reduce the severity of the consequence. For example, Hearing Countermeasures is an intervention countermeasure for the Acoustics Risk. In cases where the noise exposure experienced by the crew becomes excessive, the crew can intervene by applying ear plugs. Environmental Control can also be an Intervention Countermeasure, in cases where the noise environment becomes too loud, the intervention may be to intervene to reduce the noise.

REFERENCES

Agha NH, Mehta SK, Rooney BV, et al. (2020). Exercise as a countermeasure for latent viral reactivation during long duration space flight. *FASEB J Off Publ Fed Am Soc Exp Biol*. 2020, *34*, 2869-2881. doi: 10.1096/fj.201902327R

Alele, F. O., Malau-Aduli, B. S., Malau-Aduli, A. E. O., & J. Crowe, M. (2021). Individual anthropometric, aerobic capacity and demographic characteristics as predictors of heat intolerance in military populations. *Medicina*, *57*, 173-187. https://doi.org/10.3390/medicina57020173

Antonsen, E., Monti, A., Charvat, J., Connell, E. S., Reynolds, R. J., Abukmail, A., Marotta, K., & Brown, C. (2022). *Directed acyclic graphs: A tool for understanding the NASA spaceflight human systems risks - Human Systems Risk Board*. NASA Technical Memorandum, NASA TM – 20220015709. https://ntrs.nasa.gov/citations/20220015709

Aviation Safety Reporting Program: Prohibition against use of reports for enforcement purposes. 14 C.F.R. § 91.25 (2014).

Badhwar, G. D. (1997). The radiation environment in low-Earth orbit. *Radiation Research*, *148*, S3-10.

Basner, M., Moore, T. M., Hermosillo, E., Nasrini, J., Dinges, D. F., Gur, R. C., & Johannes, B. (2020). Cognition Test Battery performance is associated with simulated 6df spacecraft docking

performance. *Aerospace Medicine and Human Performance*, *91*, 861–867. https://doi.org/10.3357/AMHP.5602.2020

Beard, B. L. (2020a). The Cognition and Fine Motor Skills Test Batteries: Normative Data and Interdependencies. NASA TM - Technical Memorandum 20205008023.

Beard, B. L. (2020b). Characterization of how CO_2 level may impact crew performance related to the HSIA risk. NASA Technical Memorandum, NASA/TM – 20205011433. May be downloaded at https://ntrs.nasa.gov/search?q=beard%20co2

Beard, B. L., Bardina, J. E., Toscano, W. B., Odina, J. O., Winther, S. W., Griffin, E., & Krihak, M. (2023). Medical System requirements development for Lunar operations. NASA Technical Memorandum - TM2023000609. https://ntrs.nasa.gov/search?q=beard%20medical

Blue, R., Nusbaum, D., & Antonsen, E. (2022). Development of an accepted medical condition list for Exploration Medical Capability scoping. NASA Technical Memorandum, TM20190027540.

Carr, C. E. (2006). Impact of moderate elevations in CO_2 on astronauts during long-duration spaceflight on the International Space Station. NASA Internal Final Report.

Childress, S. D., Williams, T. C., & Francisco, D. R. (2023). NASA Space Flight Human-System Standard: Enabling human spaceflight missions by supporting astronaut health, safety, and performance. *NPJ Microgravity*, *9*(1), 31-37. https://doi.org/10.1038/s41526-023-00275-2

Cronyn, P. D., Watkins, S., Alexander, D. J. (2012). Chronic exposure to moderately elevated CO_2 during long-duration space flight. NASA Technical Report NASA TP-2012-217358. http://ston.jsc.nasa.gov/collections/trs/_techrep/TP-2012-217358.pdf.

Crucian, B., Babiak-Vazquez, A., Johnston, S., Pierson, D., Ott, C. M., & Sams, C. (2016). Incidence of clinical symptoms during long-duration orbital spaceflight. *International Journal of General Medicine*, *Volume 9*, 383–391. https://doi.org/10.2147/IJGM.S114188

Cucinotta, F. A., Manuel, F. K., Jones, J., Iszard, G., Murrey, J., Djojonegro, B., & Wear, M. (2001). Space radiation and cataracts in astronauts. *Radiation Research*, *156*, 460–466. https://doi.org/10.1667/0033-7587(2001)156[0460:sracia]2.0.co;2

Department of Energy (DOE) and Nuclear Regulatory Commission (NRC) Collaborative Interactions with OSHA. (n.d.). Occupational Safety and Health Administration. Retrieved December 18, 2023, from https://www.osha.gov/doe-nrc-osha

Dixit, M. (2023). *How Space Radiation Threatens Lunar Exploration*. Smithsonian Magazine. https://www.smithsonianmag.com/science-nature/how-space-radiation-threatens-lunar-exploration-180981415/

Douglas, G. L., DeKerlegand, D., Dlouhy, H., Dumont-Leblond, N., Fields, E., Heer, M., Krieger, S., Mehta, S., Rooney, B. V., Torralba, M. G., Whiting, S. E., Crucian, B., Lorenzi, H., Smith, S. M., Young, M., & Zwart, S. R. (2022). Impact of diet on human nutrition, immune response, gut microbiome, and cognition in an isolated and confined mission environment. *Scientific Reports*, *12*, 20847. https://doi.org/10.1038/s41598-022-21927-5

Douglas, G. L., Zwart, S. R., & Smith, S. M. (2020). Space food for thought: Challenges and considerations for food and nutrition on exploration missions. *The Journal of Nutrition*, *150*, 2242–2244. https://doi.org/10.1093/jn/nxaa188

EPA's Radiation Protection Standards. (2013). https://www.epa.gov/sites/default/files/2015-06/documents/402f12002_0.pdf

Gabel, L., Liphardt, A.-M., Hulme, P. A., Heer, M., Zwart, S. R., Sibonga, J. D., Smith, S. M., & Boyd, S. K. (2022). Pre-flight exercise and bone metabolism predict unloading-induced bone loss due to spaceflight. British Journal of Sports Medicine, 56(4), 196–203. https://doi.org/10.1136/bjsports-2020-103602

Garrett-Bakelman, F. E., Darshi, M., Green, S. J., Gur, R. C., Lin, L., Macias, B. R., McKenna, M. J., Meydan, C., Mishra, T., Nasrini, J., Piening, B. D., Rizzardi, L. F., Sharma, K., Siamwala, J. H., Taylor, L., Vitaterna, M. H., Afkarian, M., Afshinnekoo, E., Ahadi, S., … Turek, F. W. (2019). The NASA twins study: A multidimensional analysis of a year-long human spaceflight. *Science*, *364*, 144-165. https://doi.org/10.1126/science.aau8650

Gertz, M., Chin, C., Tomoiaga, D., Chang, C., Butler, D.J., Afshinnekoo, E., Bezdan, D., Schmidt, M.A., Melnick, A.M., Garrett-Bakelman, F., Crucian, B., Stuart, M.C., Zwart, S.R., Smith, S.M., Meydan, C, Mason, C.E. (2020). Multi-Omic, single-cell, and biochemical profiles of astronauts guide pharmacological strategies for returning to gravity. Cell Reports 33, 10-28. https://www.cell.com/cell-reports/pdf/S2211-1247(20)31418-2.pdf.

Goldhagen, P. (2015). Use of Cosmic Ray Neutron Data in Nuclear Threat Detection and Other Applications. *Neutron Monitor Community Workshop*.

Grimm, D., Schulz, H., Krüger, M., Cortés-Sánchez, J. L., Egli, M., Kraus, A., Sahana, J., Corydon, T. J., Hemmersbach, R., Wise, P. M., Infanger, M., & Wehland, M. (2022). The fight against cancer by

microgravity: The multicellular spheroid as a metastasis model. *International Journal of Molecular Sciences*, *23*(6), 3073-3118. https://doi.org/10.3390/ijms23063073

Houerbi, N., Mason, C.E., Schmidt, M.A., et al (2023). Proteomics Analysis from blood plasma and exosomes of I4 astronauts reveals distinct responses after spaceflight. *Aerospace Med Hum Perform, 94*, 185-87.

Human System Risk Board. (2023, September 12). NASA.Gov. https://www.nasa.gov/directorates/esdmd/hhp/human-system-risk-board/

IND Safety Reporting. 21 C.F.R § 312.32 (a) (2023).

Jones, J. A., McCarten, M., Manuel, K., Djojonegoro, B., Murray, J., Feiversen, A., & Wear, M. (2007). Cataract formation mechanisms and risk in aviation and space crews. *Aviation, space, and environmental medicine*, *78*, A56-A66.

Jones, J., Montesinos, C., Karouria, F., Popov, D., Boreham, D., Cristea, O., & Greenberger, J. (2018a). Low dose rate and sporadic high LET radiation. In *Radiobiology of Space Radiation*.

Jones, J. A., Karouia, F., Cristea, O., Casey, R. C., Popov, D., & Maliev, V. (2018b). Ionizing Radiation as a Carcinogen. In *Comprehensive Toxicology* (pp. 183–225). Elsevier. https://doi.org/10.1016/B978-0-12-801238-3.64295-2

Jones, J. A., Karouia, F., Pinsky, L., & Cristea, O. (2019). Radiation and Radiation Disorders. In *Principles of Clinical Medicine for Space Flight* (pp. 39–108). Springer New York. https://doi.org/10.1007/978-1-4939-9889-0_2

Kim, J., Mason, C.E., Schmidt, M.A., et al. (2023). Inspiration4: Comprehensive and integrative single cell multiomics analysis of the immune system of SpaceX Inspiration4 mission crews. *Aerospace Med Hum Perform, 94*, 185-87.

Lake, R. C., Harrivel, A. R., & Reichard, J. F. (2023). Exploration Medical Capability IMPACT medical database–Medical Item Database (MedID) content development methods. NASA Technical Memorandum, TM-20230005442.

Law, J., Van Baalen, M., Foy, M., Mason, S. S., Mendez, C., Wear, M. L., Meyers, V. E., & Alexander, D. (2014). Relationship between carbon dioxide levels and reported headaches on the International Space Station. *Journal of Occupational & Environmental Medicine*, *56*, 477–483. https://doi.org/10.1097/JOM.0000000000000158

Mansi, T., Passerini, T., & Comaniciu, D. (2020). *Artificial Intelligence for Computational Modeling of the Heart*. Elsevier. https://doi.org/10.1016/C2017-0-03208-1

Marge, M. (2021). Summary Report of the CSF/MITRE Workshop to Create a Human Research Program for Spaceflight Participants in the Commercialization of Space. Retrieved Jan 3, 2024 at https://www.commercialspaceflight.org/news_events/2021-summary-report-of-the-csf-mitre-workshop-to-create-a-human-research-program-for-spaceflight-participants-in-the-commercialization-of-space/

Marge M. (2022). Preparing civilians to travel, live, and work in space: A human research agenda. New Space, Vol. 10, No. 3, 22-26.

Marge M. Preparing individuals with disabilities for space travel and habitation. Disabil Health J. 2022 Apr;15(2):101228. doi: 10.1016/j.dhjo.2021.101228. Epub 2021 Oct 23. PMID: 34711524.

Marge M. (2023). Health research is needed now before sending civilians to space. Scientific American, Opinion, March 22.

Marge, M. (2023a). Protecting the Health and Safety of Civilians in the Future Space Workforce. *Journal of Space Safety Engineering*, *10*(1), 22–26. https://doi.org/10.1016/j.jsse.2023.01.004

Mason, C.E., Schmidt, M.A., et al. (2023). A Biobank to support the federated study of private astronauts. *Aerospace Med Hum Perform, 94*, 185-87.

McLaughlin, M. F., Donoviel, D. B., & Jones, J. A. (2017). Novel indications for commonly used medications as radiation protectants in spaceflight. *Aerospace Medicine and Human Performance*, *88*, 665–676. https://doi.org/10.3357/AMHP.4735.2017

Mullenax, C. & Beard, B. L. (2022). Increasing cognitive reserves with software. NASA Technical Memorandum, NASA TM- 20220016604.

Nath, S. V., Van Schalkwyk, P., & Isaacs, D. (2021). *Building industrial digital twins: Design, develop, and deploy digital twin solutions for real-world industries using Azure digital twins*. Packt Publishing Ltd.

Overby, E., Mason, C.E., Schmidt, M.A., et al. (2023). A comprehensive report of all biospecimens and multiomic measurements from the Inspiration4 Mission. *Aerospace Med Hum Perform, 94*, 185-87.

Park, J., Mason, C.E., Schmidt, M.A., et al. (2023). Spatial transcriptomics and multiomics reveal Human skin responses to spaceflight. *Aerospace Med Hum Perform, 94*, 185-87.

Paulus, M. P., Potterat, E. G., Taylor, M. K., van Orden, K. F., Bauman, J., Momen, N., Padilla, G. A., & Swain, J. L. (2009). A neuroscience approach to optimizing brain resources for human

performance in extreme environments. *Neuroscience & Biobehavioral Reviews*, *33*, 1080–1088. https://doi.org/10.1016/j.neubiorev.2009.05.003

Ploutz-Snyder, L. (2016). Evaluating countermeasures in spaceflight analogs. *J Appl Physiol*, *120*, 915–921. https://doi.org/10.1152/japplphysiol.00860.2015.

Rahman, S. A., Sullivan, J. P., Barger, L. K., St. Hilaire, M. A., O'Brien, C. S., Stone, K. L., Phillips, A. J. K., Klerman, E. B., Qadri, S., Wright, K. P., Halbower, A. C., Segar, J. L., McGuire, J. K., Vitiello, M. V., de la Iglesia, H. O., Poynter, S. E., Yu, P. L., Sanderson, A. L., Zee, P. C., … Lockley, S. W. (2021). Extended work shifts and neurobehavioral performance in resident-physicians. *Pediatrics*, *147*(3), 1-12. https://doi.org/10.1542/peds.2020-009936

Reddy, A., Conde, C., Peterson, C., & M Nugent, K. (2022). Residential radon exposure and cancer. *Oncology Reviews*, *16*, 558-566. https://doi.org/10.4081/oncol.2022.558

Riva, P., Rusconi, P., Pancani, L., & Chterev, K. (2022). Social isolation in space: An investigation of LUNARK, the first human mission in an Arctic Moon analog habitat. *Acta Astronautica*, *195*, 215–225. https://doi.org/10.1016/j.actaastro.2022.03.007

Ronca, A. E., Moyer, E. L., Talyansky, Y., Lowe, M., Padmanabhan, S., Choi, S., Gong, C., Cadena, S. M., Stodieck, L., & Globus, R. K. (2019). Behavior of mice aboard the International Space Station. *Scientific Reports*, *9*(1), 4717. https://doi.org/10.1038/s41598-019-40789-y

Sanderson-November, M., Silver, S., Hooker, V., & Schmelz, M. (2022). Biorepository best practices for research and clinical investigations. *Contemporary Clinical Trials*, *116*, 106572. https://doi.org/10.1016/j.cct.2021.106572

Sawka, M. N., Cheuvront, S. N., & Kenefick, R. W. (2015). Hypohydration and human performance: Impact of environment and physiological mechanisms. *Sports Medicine*, *45*, 51–60. https://doi.org/10.1007/s40279-015-0395-7

Schmidt, M. A., Goodwin, T. J. (2013). Personalized medicine in human space flight: Using omics-based analysis to develop individualized countermeasures that enhance astronaut safety and performance. *Metabolomics, 9*, 1134-1156.

Schmidt, M.A., Goodwin, T.J., Pelligra, R. (2016). Incorporation of omics analyses into artificial gravity research for space exploration countermeasure development. *Metabolomics* 12, 1-15.

Schmidt, M. A., Meydan, C., Schmidt, C. M., Afshinnekoo, E., & Mason, C. E. (2020a). Elevation of gut-derived p-Cresol during spaceflight and its effect on drug metabolism and performance in astronauts. Downloaded on Jan 3, 2024 at

https://web.archive.org/web/20210428231307id_/https://www.biorxiv.org/content/biorxiv/early/2020/11/17/2020.11.10.374645.full.pdf.

Schmidt, M. A., Meydan, C., Schmidt, C. M., Afshinnekoo, E., & Mason, C. E. (2020b). The NASA Twins Study: The effect of one year in space on long-chain fatty acid desaturases and elongases. *Lifestyle Genomics*, *13*(3), 107–121. https://doi.org/10.1159/000506769

Schmidt, M. A., Schmidt, C. M., Hubbard, R. M., & Mason, C. E. (2020). Why personalized medicine is the frontier of medicine and performance for humans in space. *New Space*, *8*, 63–76. https://doi.org/10.1089/space.2019.0037

Schmidt, M. A., Jones, J. A., & Mason, C. E. (2023). Optimizing human performance in extreme environments through precision medicine: From Spaceflight to High-Performance Operations on Earth. *Cambridge Prisms: Precision Medicine*, *1*, e27. https://doi.org/10.1017/pcm.2023.16

Schmidt, C. M., Schmidt, M. A., Patterson, T. (2023). Building an astronaut digital twin: Practical applications for advancing human spaceflight. Paper presented at Building a Space Faring Civilization: Advancing the Renaissance of Science, Medicine, and Human Performance in Civilian Spaceflight. International Symposium, Florence, Italy. Sept 13-15, 2023.

Shelhamer, M., Bloomberg, J., LeBlanc, A., Prisk, G.K., Sibonga, J., Smith, S.M., Zwart, S.R., Norsk, P. (2020) Selected discoveries from human research in space that are relevant to human health on Earth. *NPJ Microgravity*. *12*, 5-9. doi: 10.1038/s41526-020-0095-y.

Shirah, B., Bukhari, H., Pandya, S., & Ezmeirlly, H. A. (2023). Benefits of space medicine research for healthcare on Earth. *Cureus, 15*, 1-5. https://doi.org/10.7759/cureus.39174

Sihver, L., Ploc, O., Puchalska, M., Ambro ova, I., Kuban ak, J., Kyselova, D., & Shurshakov, V. (2015). Radiation environment at aviation altitudes and in space. *Radiation Protection Dosimetry*, *164*(4), 477–483. https://doi.org/10.1093/rpd/ncv330

Smith, S. M., & Zwart, S. R. (2021). Nutrition as fuel for human spaceflight. *Physiology*, *36*, 324–330. https://doi.org/10.1152/physiol.00011.2021

Sobel, A., & Forslay, L. (2023). Identifying neutron irradiation in space to mitigate bio-medical effects. Presented at the *International Conference on Condensed Matter Nuclear Science* in Szczecin, Poland. NASA Technical Memorandum, TM-20230005363.

Stahn, A. C., Gunga, H.-C., Kohlberg, E., Gallinat, J., Dinges, D. F., & Kühn, S. (2019). Brain changes in response to long Antarctic expeditions. *New England Journal of Medicine*, *381*, 2273–2275. https://doi.org/10.1056/NEJMc1904905

Strangman, G. E., Sipes, W., & Beven, G. (2014). Human cognitive performance in spaceflight and analogue environments. *Aviation, Space, and Environmental Medicine*, *85*, 1033–1048. https://doi.org/10.3357/ASEM.3961.2014

Stuster, J. (2010). Behavioral issues associated with long-duration space expeditions: review and analysis of astronaut journals. NASA Technical Memorandum, NASA/TM- 20120003494.

Stuster, J. (2016) Behavioral issues associated with long-duration space expeditions: Review and analysis of astronaut journals. NASA Technical Memorandum, NASA TM-2016218603.

Tafforin, C., Vinokhodova, A., Chekalina, A., & Gushin, V. (2015). Correlation of etho-social and psycho-social data from "Mars-500" interplanetary simulation. *Acta Astronautica*, *111*, 19–28. https://doi.org/10.1016/j.actaastro.2015.02.005

Tang, H., Rising, H. H., Majji, M., & Brown, R. D. (2021). Long-term space nutrition: A scoping review. *Nutrients*, *14*(1), 194-224. https://doi.org/10.3390/nu14010194

Tierney, B., Mason, C.E., Schmidt, M.A., et al. (2023). The metagenomic and metatranscriptomic architecture of human and spacecraft microbiome alterations during short-term spaceflight. *Aerospace Med Hum Perform 94*, 185-87.

Von Braun, W., & Ryan, C. (1954). Can We Get to Mars? *Collier's Weekly*, 26.