Exploration Medical Capability
Evidence Library Methods

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November 2023
Revision B

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

Exploration Medical Capability Evidence Library Methods

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Change/ Revision	**Date**	**Description of Change**	**Pages Affected**
Baseline	27 January 2021	• Informing IMPACT 1.0 project deliverables	All
Revision A	28 February 2022	• Evidence Library project deliverables complete.	All
Revision B	14 November 2023	• Evidence Library project deliverables updated. Administrative. Updated the condition list with deletions of ICL 121 and 79, updated total number of conditions throughout to 119. Renumbered figures and sections that were deleted. • Section 3.1.2. Added LDLOS runs as a source that informed changes to the EvLib condition list • Section 3.1.2.5. Updated the version history for IMPACT 1.0 to include the most recent changes to the conditions list. • TABLE 2 ICL 1.0 VERSION 1.0 to 3.2, CONDITION ADDITION AND REMOVAL RATIONALE changes o Added ICL 36a and 36b (Lunar Dust) with rationales o Deletion of ICL 121 (adjustment disorder) and 79 (Reactive Airway) with rationales • Section 3.4.1. RTDC. Made changes to the RTDC surrogates to describe the work done by the RTDC group. Although this work applies to IMPACT 1.1, the definition changes have been accepted by ExMC leadership and have been implemented in some IMPACT 1.0 CLiFFs. • Section 3.4.1.2. TTL. Changes made to reflect the updates incorporated in LD 149 for IMPACT 1.0. These include a description of the method for changing TI% from a constant value throughout CP2 to a linear decrement from the beginning of CP2 to the beginning of CP3. • Section 3.6.1.4. TI as a discrete value. This section was largely deleted as the rationale for using a discrete value for TI rather than a range was not thought to be accurate. Also, a standard method for defining the end of CP2 duration is defined. • Table 10. CAPABILITY RESOURCE TABLE MODEL PARAMETERS. o Updated to reflect changes made by Tiger teams led by Lynn Boley to update definitions and resource lists that were incorporated in LD 149, including dose frequency and duration.	All

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		• Section 5 Limitations.
		  o Section 5.1.1. General Considerations. A limitation was added concerning the lack of confidence intervals for all metrics.
		  o Section 5.1.4. Task Impairment. A limitation was added that addressed the possibility of reassignment of crew tasks lowering the impact of task impairment. TI does not currently account for possible redistribution of tasks within the crew after a condition causing task impairment occurs.
		  o Section 5.1.6. CRT's. A limitation (#8 on rev A) was deleted. It commented that broad ranges of CP2 duration will affect resources. The description of the limitation was confusing, possibly inaccurate, and, in any case, unactionable.
		• Section 6. Recommendations.
		• Section 6.5. Task Impairment. A recommendation was added to consider making TI% a range rather than a discrete value. This would better characterize the uncertainty in this parameter.
		• Appendices. Many minor updates to reflect the addition (ICL 36a and 36b) and deletion (ICL 121 and 79) of medical conditions were made.	

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1.0 INTRODUCTION

Engineering risk reduction first requires the identification of material, structural, and system failure characteristics. These limits are used to estimate the risk of overall mission loss and mitigate design flaws. Similarly, medical risk reduction requires identification of potential medical conditions, utilizing probability of disease occurrence and knowledge of disease progression, to determine crewmember quality of life or risk of mortality. While terrestrial medical risk reduction typically involves the provision of adequate supplies and training of personnel, spaceflight is further limited by mass and volume constraints, stowage, power, and microgravity. Exploration-class space missions, defined as missions outside of low-Earth orbit (LEO) of increasing duration (e.g., Lunar and Martian missions), may also prevent resupply opportunities and timely return to definitive care.

The IMPACT (Informing Mission Planning via Analysis of Complex Tradespaces) project seeks to inform medical system design by computing minimization of medical risk with respect to engineering constraints for a given Design Reference Mission (DRM). This requires translation of medical risk drivers into engineering risk language. It also requires a robust basis of medical data for applicable conditions, in representative populations, to inform expected morbidity risk, progression, and outcome with or without treatment. These clinical data have been provided by the Clinical and Science Team of the Exploration Medical Capability (ExMC) Element and are summarized in this Evidence Library (EL) methods document.

1.1 PURPOSE

The purpose of this document is to describe the EL clinical data, the general methods employed to collect those data, and a brief overview of how the IMPACT project will use the data via the MEDPRAT (Medical Extensible Dynamic Probabilistic Risk Assessment Tool) computational engine. For a full overview of how IMPACT functions, how MEDPRAT operates, details on specific medical conditions/data points, or additional details on any other aspect of the project, please refer to the references listed in Appendix A Reference Documentation.

1.2 SCOPE

This document will detail the Evidence Library clinical data required to initially populate the IMPACT Medical Database (IMPACT-MD) and outline the general methods and expertise required to obtain those data. Configuration management of the clinical data once imported into the IMPACT-MD is outside the scope of this document. Refer to the IMPACT-MD Project Plan for more information.

1.3 RESPONSIBILITY AND CHANGE AUTHORITY

This document is under Configuration Management control of the Exploration Medical Capability Element Control Board (ExMCCB). Changes to this document will result in the issuance of change pages or a full re-issue of the document.

2.0 CLINICAL DATA OVERVIEW

2.1 EVIDENCE LIBRARY OVERVIEW

The purpose of the EL is to acquire and maintain the medical evidence that allows exploration-class mission trade space assessment using the IMPACT tool suite. Due to project and schedule constraints, medical evidence collection was based on data in the Integrated Medical Evidence Database (iMED) acquired from Crew Health & Safety (CHS). The architecture and information from this dataset were utilized and updated where necessary to obtain the highest fidelity data possible. More information on the iMED architecture and legacy medical evidence can be found in the Integrated Medical Model (IMM) Conceptual Document and the IMM Clinical Finding Forms Overview referenced in Appendix A Reference Documentation

iMED data architecture was conserved, when possible, to ensure compatibility with the MEDPRAT tool and to retain legacy methodologies that could not be duplicated in this initial effort due to project cost and schedule constraints. However, changes to the iMED data architecture were necessary to accommodate the incidence data structure, Task Impairment (TI), and Capability Resource Tables (CRTs). Branching and lockdown mechanics were conserved. Legacy iMED medical evidence was evaluated and overhauled. Legacy data were conserved when appropriate; however, extensive updates were made to existing iMED conditions in accordance with new best and worst-case scenario definitions and current medical literature. New conditions were also created, which required novel data. Updates to the medical evidence were made on a condition-by-condition basis and relied on the following factors: applicability of current data to an exploration environment, age and credibility of supporting evidence and availability of newer standard clinical regimens and data, MEDPRAT software architectural limitations, and cost/schedule constraints. For more detailed information, interested readers should refer to the IMPACT-MD Project Management Plan and Project Technical Requirements Specification (PTRS) for the IMPACT tool suite documents referenced in Appendix A.

Evidence Library data used to inform the IMPACT 1.0 tool suite is subject to verification and validation (V&V) as set forth in NASA-STD-7009A, with requirements for this V&V as defined per IMPACT Project Technical Requirements. Several factors outlined in this document will be used during V&V to interpret how the EL dataset meets or does not meet these requirements, including the qualification of personnel used to collect and record the data, the methodology employed to demonstrate traceability of evidence to its source, level of peer review performed on the completed condition datasets, and the overall quality of the evidence provided.

2.2 MEDICAL EVIDENCE UPDATE OVERVIEW

For IMPACT 1.0, the EL team collected and documented the medical evidence in 119 Clinical Finding Forms (CLiFFs) and delivered these data to the IMPACT-MD during FY20-FY23. The EL team includes subject matter experts (SMEs) encompassing a diverse array of terrestrial medical specialties, aerospace medicine, research and design medicine, pharmacy,epidemiology, statistics, library science, evidence-based medicine, and computational modeling. The training and expertise of this team were leveraged to design the methods outlined below and applied to the rapid systematic review process specific to each CLiFF. Upon finalization of the IMPACT 1.0 Medical Conditions List (ICL 1.0), the EL team completed a rapid systematic review to collect data on incidence rates, clinical phase duration, and outcomes for both treated and untreated condition states. Additionally, clinicians familiar with terrestrial management of these conditions used practice guidelines and clinical experience to assign the capabilities needed to treat each condition and the resources needed to support each capability.

The evidence serves as the source of medical data for the IMPACT tool suite. The EL team has delivered the following:

1) The IMPACT 1.0 Medical Conditions List (ICL 1.0) (Section 3.1)

A limit of 120 conditions was established by project leadership as a schedule- and resource-feasible goal for IMPACT version 1.0. Several conditions were added to the original list, and some were later deleted, leaving 119. However, in addition to the 119 medical conditions applicable to exploration-class spaceflight missions named in the condition titles on this list, ICL 1.0 includes ‘Conditions Not Explicitly Stated’ (CNES) that were encompassed by the definitions (ICL 1.0 v3 and associated CNES in Appendix C IMPACT 1.0 Condition List (ICL 1.0). The medical condition definitions were refined from legacy iMED data in order to: 1) better reflect the anticipated medical needs of crewed exploration-class spaceflight missions, 2) incorporate current medical literature and medical practice, and 3) encompass the capabilities and resources needed to treat the identified conditions. Condition definitions support the IMM legacy architecture for severity through inclusion of best-case/worst-case scenarios as described in Section 3.1.3.

2) Condition specific parameters and medical evidence informing the MEDPRAT computational engine:

   a. Incidence (Sections 3.4 and 4.2)

   b. Best and worst-case scenario probability (Sections 3.1.3 and 4.3)

   c. Clinical phase durations (Section 3.5)

   d. Mission End States (Section 3.4)

      i. Probability of Removal to Definitive Care (RTDC)

      ii. Probability of Loss of Crew Life (LOCL)

   e. Task Impairment (TI) (Section 3.6)

   f. Capability and Resource Tables (CRTs) (Section Clinical Capabilities, Resources, Resource Equivalence, and Resource to Capability Matrices)

CRTs contain the clinical capabilities required for diagnosis, treatment, and long-term management of each condition as well as primary and alternate resources used by each capability.

3) IMPACT condition groupings and crew characteristics (Section 3.3.1)

4) Level of Confidence scores to capture the degree of confidence the EL team has in the data supporting the above items (Section Grading of Evidence (Level of Confidence) Method)

5) References to allow future researchers to trace all CLiFF evidence to its source (Section

6) Maintenance of References)

Data were collected and recorded in CLiFFs that permit traceability from source material to data points and from data points to parameters in the MEDPRAT computational engine. An example of two CLiFFs and their associated medical evidence, formatted for review outside of the IMPACT-MD, can be viewed in Appendix B. These data are stored in the IMPACT-MD. A virtual repository, the IMPACT-MD, is used to store, manage, and provide clinical and engineering data for medical conditions, capabilities, and resources. IMPACT-MD contains two sub-components: Evidence Library and the Medical Item Database (MedID). MedID houses the engineering data and physical attributes that describe the quantitative aspects of the medical resource items (e.g., mass, volume, power, etc.), as well as Figure of Merit (FoM) information to characterize operational environment features associated with each of the resource items identified in the CRTs. The EL houses all other clinical data. Figure 1 Integration of the IMPACT Tool Suite illustrates the role of IMPACT-MD within the IMPACT tool suite.

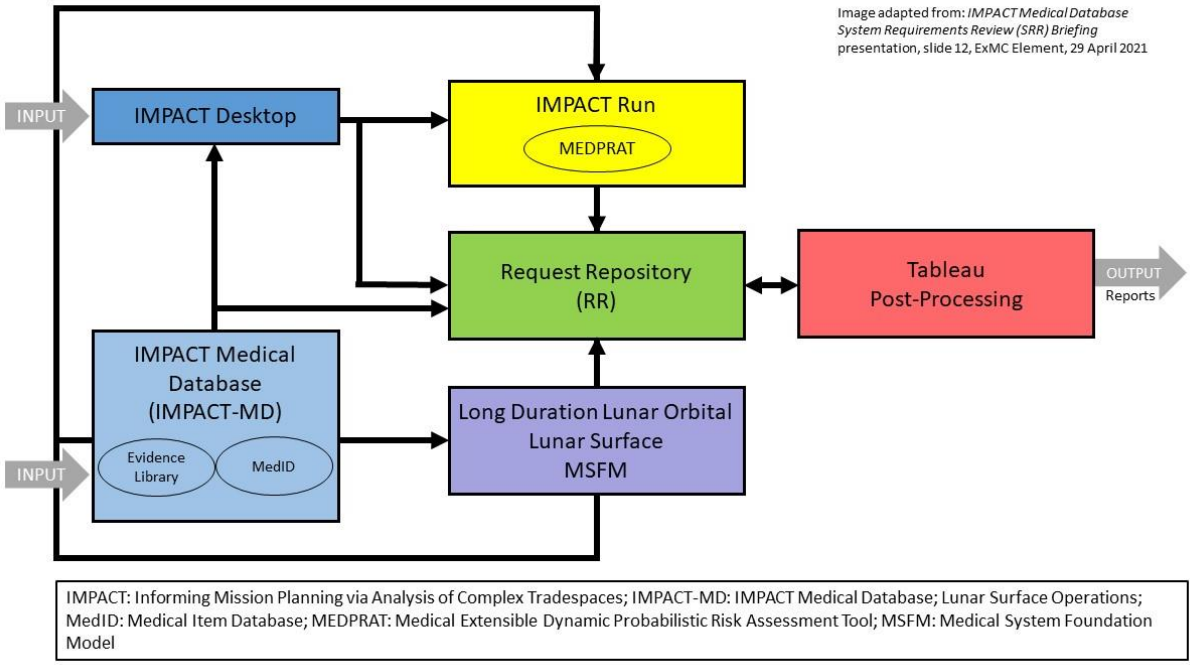


Figure 1 Integration of the IMPACT Tool Suite

3.0 MEDICAL EVIDENCE METHODS

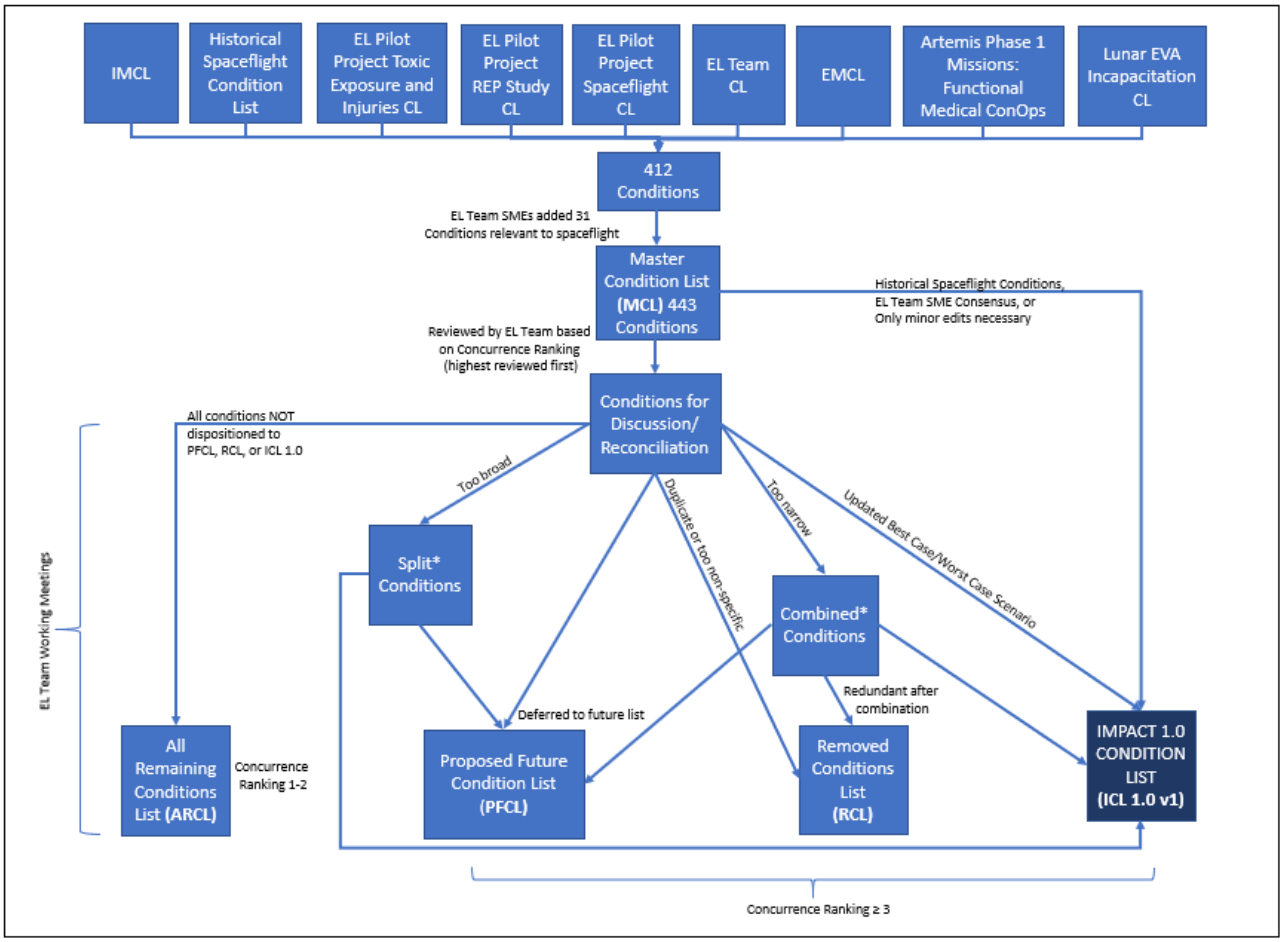
3.1 CONDITION LIST AND DEFINITIONS

3.1.1 Overview

CONDITION LIST PRODUCTS:

The condition list is the basis for all EL efforts. The EL team has prepared 4 lists as products of this effort (Figure):

1. IMPACT 1.0 Medical Conditions List (ICL 1.0 v1, v2, v3, v3.1, v3.2)
2. Proposed Future Conditions List (PFCL)
3. Removed Conditions List (RCL)
4. All Remaining Conditions List (ARCL)



All conditions included in ICL 1.0 had best/worst-case scenario definitions updated. IMCL: IMM Medical Condition List; EL: Evidence Library; CL: condition list; EMCL: Exploration Medical Condition List; ConOps: concept of operations; EVA: extravehicular activity. *Additional conditions added during splitting/combining process.

Figure 2 IMPACT 1.0 Medical Condition List Refinement Methodology Overview

The "IMPACT 1.0 Medical Conditions List" (ICL 1.0) contains 119 conditions, for which the EL team collected relevant medical evidence. As described above, the initial limit of 120 conditions was established by project leadership as a schedule- and resource-feasible goal for IMPACT version 1.0. Additions and deletions were later made during reviews and verification, leaving a total of 119. Conditions on the ICL 1.0 reflect a representative sample of conditions and exposures relevant to characterize an exploration class mission for purposes of IMPACT 1.0 demonstration. The ICL 1.0 is included in Appendix C.

The "Proposed Future Conditions List" (PFCL) contains conditions that the EL team felt were relevant to this project but were excluded from ICL 1.0 due to the aforementioned project time and resource constraints. These conditions were felt to be less likely to occur and/or less severe. Many of these conditions have direct relevance for exploration missions, particularly to Mars DRMs. Inclusion of these additional conditions is recommended for future iterations of IMPACT, but beyond the scope of this initial effort. The PFCL is included in Appendix E Proposed Future Conditions List (PFCL)

The "Removed Conditions List" (RCL) is included for transparency in Appendix F. These are conditions that were identified as potential candidates during initial list development, but were subsequently removed from consideration because:

- They were already covered in existing ICL 1.0 condition definitions, or
- They were non-specific, limiting ability to identify supporting medical literature, obtain incidence data, assign medical resources, and/or assign associated Task Impairment values. Note that for most of these conditions similar, but more specific, conditions were included in ICL 1.0.

The "All Remaining Conditions List" (ARCL) contains remaining conditions that were considered for ICL 1.0 but were not included on any of the aforementioned lists. These conditions should also be considered for inclusion in subsequent iterations of IMPACT-MD and IMPACT but are a lower priority than the PFCL conditions. The ARCL is included in Appendix G All Remaining Conditions List (ARCL)

CONDITION LIST NOMENCLATURE:

To enable a traceable unique identifier for each condition, across the various lists, a standard nomenclature was devised. Conditions are numbered, with the abbreviation for the list appearing before the number of the condition. For example, conditions on the ICL 1.0 were numbered ICL1, ICL2, ICL3, etc. One exception is that ICL36, Lunar Dust Exposure, was sub-categorized into ICL36a and ICL36b in order to characterize the difference in risk between crewmembers performing EVAs and those remaining inside a lunar habitat. Likewise, conditions on the other product lists (PFCL, RCL, ARCL) were named in the same manner with the appropriate list acronym preceding the condition number. The same is true for the Master Condition List (MCL).

3.1.2 IMPACT 1.0 Medical Conditions List Refinement Methodology

The ICL 1.0 development effort initially proceeded in the context of a 210-day mission to cis-lunar space, a DRM analog for future Mars missions. This mission includes 150-180 days in transit or halo orbit and 30-60 days on the lunar surface, with both transit/orbital and surface operations inclusive of extravehicular activity (EVA). In addition, modifications to the ICL were made while evaluating the Long Duration Lunar Orbital Lunar Surface (LDLOLS) DRM which uses a one-year mission with 36 EVAs. The exposures captured in these DRMs informed the team on which conditions to prioritize.

Since multiple groups within NASA are involved in developing systems to support human health during spaceflight, several condition lists currently exist. The first step in creating ICL 1.0 v1 combined the conditions from the lists found in TABLE 1 below to generate a composite list of 412 conditions.

TABLE 1 SOURCES CONTRIBUTING TO ICL 1.0 v1

Condition List Title	Description
IMM Medical Conditions List (IMCL)[1]	Condition list informing the iMED database (as previously described in this document).
IMCL Historical Spaceflight Condition List[2]	Those iMED conditions known to have occurred inflight based on ISS and Shuttle data providedby the NASA Lifetime Surveillance of Astronaut Health (this does not include terrestrial-based conditions thought to be related to spaceflight). This list is a subset of the conditions listed in theIMCL.

[1] IMM Medical Conditions List. IMM Project, Crew Health & Safety. IMM-GEN 309, Rev 1.
[2] Lifetime Surveillance of Astronaut Health. https://lsda.jsc.nasa.gov/LSAH/LSAH_Home

Condition List Title	Description
Evidence Library Pilot Project Toxic Exposures andInjuries Condition List[3]	Medical (Emergency Medicine, Internal Medicine, Aerospace Medicine) SME-derived list ofplausible toxic exposures and injuries during exploration missions.
Evidence Library Pilot Project Rochester Epidemiology (REP)[4] Study Condition List[3]	The REP is a large, well-known clinical database based in Olmsted County, Minnesota. The REP study identified an astronaut analog population within the REP database and determined the incidence of conditions in a 3-year period based on International Classification of Disease (ICD) codes. This list of 1393 ICD codes corresponding to clinical diagnoses were reviewed toidentify medical conditions that could occur inflight for inclusion in the master condition list.
Evidence Library Pilot Project Spaceflight ConditionList[3]	Medical (Emergency Medicine, Internal Medicine, Aerospace Medicine) SME-derived list ofconditions that result from human exposure to the spaceflight environment.
The EL Team Condition List[3]	SME-derived list of conditions anticipated to occur during an exploration mission. SMEs included members of the Exploration Medical Capability (ExMC) Clinical & Science Team.
Exploration Medical Condition List (EMCL)[5]	An edited list of conditions, based on the IMCL, to address concerns during exploration missions (Constellation-era).
Artemis Phase I: Functional Medical Concept ofOperations Condition List[6]	The draft medical concept of operations document for the Artemis Phase I Mission.
Lunar Extravehicular Activity (EVA) IncapacitationCondition List[7]	An edited list of conditions, based on the IMCL, to address conditions that may lead to incapacitation during lunar surface EVAs. This list contained the original IMCL as well as newconditions of concern. Only the new conditions were abstracted for inclusion.

An additional 31 conditions relevant to spaceflight were added based on SME input from the EL Team (e.g., Behavioral Health and Performance (BHP) – Grief Reaction, EVA Related Shoulder Injury, GravityWell – Entry Motion Sickness, Gravity Well – Neurovestibular Disturbance, Pulmonary Barotrauma). These additions created a working Master Condition List (MCL).

The MCL of 443 conditions was then reviewed by the EL team to prioritize conditions for inclusion in ICL 1.0 v1 (Figure). The MCL is provided in Appendix D Master Condition List (443 conditions):.

3.1.2.1 EL Team SME Backgrounds

The EL condition list development team represented a collaborative effort inclusive of SMEs from thefollowing backgrounds:

- Physician – Aerospace Medicine, Anesthesiology, Family Medicine, Internal Medicine, Emergency Medicine, Pain Medicine, Pathology, Physical Medicine & Rehabilitation, Psychology, Rheumatology, Sports Medicine, Obstetrics and Gynecology (Women's Health), and Public Health.

[3] Evidence Library Pilot Project Final Report. ExMC Element, Human Research Program. Unpublished.
[4] Rochester Epidemiology Project. https://rochesterproject.org/
[5] Exploration Medical Condition List, Rev C. ExMC Element, Human Research Program. JSC-65722.
[6] Draft: Artemis Phase I: Functional MedicalConcept of Operations Condition List. Artemis Program Medical Officer, SpaceMedicine Operations. Unpublished.
[7] Draft: Lunar EVA Incapacitation Condition List. EVA Incapacitated Crew Rescue Working Group (SA). Unpublished.

- Nursing – Registered Nurse, Master of Science in Nursing (emergency nursing, critical care,nursing informatics).
- Epidemiology.
- Pharmacy.
- Clinical Science

In addition, the EL condition list development team conferred with spaceflight and medical operations SMEs in the following fields regarding relevant conditions as described:

- Dentistry – regarding all dental conditions.
- Johnson Space Center (JSC) BHP – regarding all behavioral health-related conditions. BHP prioritized 8 conditions as candidates for inclusion in the ICL 1.0 v1 and assisted in writing the best/worst-case scenarios for these conditions.
- JSC Undersea and Hyperbaric Medicine, the EVA Physiology Laboratory, and JSCMusculoskeletal Medicine and Rehabilitation – regarding EVA related conditions.
- JSC Undersea and Hyperbaric Medicine and Orion/Multipurpose Crew Vehicle Operations –regarding altitude illness.
- JSC Optometry – regarding eye conditions.
- Aerospace Technology, Technical Management – regarding Lunar/Martian dust exposure.
- Aerospace Technology, Life Sciences Research – regarding toxic exposures and combustion products.

3.1.2.2 Master Condition List Stratification

Conditions that have occurred historically in spaceflight were considered the highest priority for inclusion in the ICL 1.0. All iMED conditions that have occurred in-flight were included in the ICL 1.0. The next consideration was for conditions that met a high degree of concurrence among the 9 aforementioned condition source lists (TABLE 1). Each list on which a condition appeared was counted towards that condition's concurrence ranking (i.e., if a condition occurred on 5 of the 9 lists, it received a concurrence ranking of 5). The maximum possible concurrence ranking was a score of 9. Concurrence rankings spanned from 1-9. Conditions with a concurrence ranking of 3 or higher were discussed in prioritization working meetings by the EL team, led by the condition list lead (see details in "EL Team Working Meetings" section below). All conditions with a concurrence ranking of 3 or higher were dispositioned to one of the following lists: ICL 1.0 v1, PFCL, or RCL. The ARCL contains only conditions with a concurrence ranking of 1-2.

3.1.2.3 Initial Categorization of Conditions from the MCL

Review of the MCL occurred sequentially, starting with conditions with the highest concurrence ranking. EL team SMEs reviewed the list and provided comments for each of the conditions. Each condition was then initially categorized into one of the following (Figure 2):

1. ICL 1.0 v1: (Any of the following criteria)
    a. If all SMEs supported inclusion of the condition in the ICL 1.0, with no dissenting opinions, then the condition was included.
    b. If a condition needed only minor edits (e.g., renaming of the condition "Visual Impairment/Intracranial Pressure Syndrome" to reflect the current nomenclature, "Spaceflight-Associated Neuro-ocular Syndrome"), and SMEs otherwise unanimously supported inclusion, then the change was made, and the condition was included.

2. Conditions for discussion/reconciliation:

    a. If EL team SMEs provided *any* comment with constructive feedback on a condition, it was initially included in this section. SME comments primarily encompassed conditions being too broad and requiring further stratification, conditions being too narrow and allowing combination with other relevant conditions (see "Split and Combined Conditions" below), or conditions in need of revised best-case and worst-case scenario definitions.

SPLIT AND COMBINED CONDITIONS

Many conditions for discussion/reconciliation were similar or overlapped. In some cases, EL team SMEs recommended combining conditions, often due to similarity in medical management or perceived lack of granularity in supporting literature. Prospective combination conditions were placed on this list (e.g., shoulder, elbow, and wrist sprain/strain were each placed on this list and ultimately combined in the condition "Upper Extremity Sprains/Strains." After combination, shoulder, elbow, and wrist sprain/strain were each moved to the RCL). All conditions that were combined were tracked and dispositioned to ICL 1.0 v1, PFCL or RCL. After combination, redundant conditions were moved to the RCL. Similarly, some of the conditions for discussion/reconciliation were felt to be too broad by EL team SMEs and were recommended to be divided into multiple conditions (e.g., Abdominal Injury was divided into 2 separate conditions, blunt and penetrating abdominal trauma). All split conditions were dispositioned to ICL 1.0 v1, PFCL, or RCL.

3.1.2.4 EL Team Working Meetings

All conditions were initially reviewed individually by EL team SMEs who provided annotations to the condition list lead (a Family Medicine-, Sports Medicine-, and Aerospace Medicine-trained physician). The condition list lead then worked to reconcile the comments of the EL team (including updating condition titles and best/worst-case scenarios, splitting conditions, or combining conditions to reflect reviewer comments). The EL team then met for approximately 25 hours of consensus meetings. All conditions with a concurrence rating of 3 or higher were discussed to reach consensus in these meetings. Select conditions with a concurrence rating of 1 or 2 were also discussed to reach consensus due to potential relevance for the cis-lunar DRM for IMPACT 1.0 (e.g., "EVA-Related Dehydration"). Notably, conditions were created by EL team consensus during these meetings to fill gaps unaddressed by the original 443 conditions in the MCL. Some of these added conditions were ultimately included on the ICL1.0 v1 (e.g., many EVA-related conditions and BHP conditions); others were deferred to the PFCL (e.g., "Chronic Diarrhea"). During these meetings, the condition titles and best/worst-case scenario definitions of all ICL 1.0 v1 conditions, and several of the PFCL conditions were updated/created according to EL team SME input and consensus.

3.1.2.5 Disposition of Conditions from Initial Categorization to Final Condition Lists

All conditions were ultimately dispositioned to one of the following 4 lists: ICL 1.0 v1, PFCL, RCL, ARCL (sometimes via the intermediary step of splitting or combining conditions where appropriate) as depicted in Figure . Note that additional conditions were created during the EL Team Working Meetings process detailed above, thus more than the 443 original conditions from the MCL exist across the product lists.

1. All Remaining Conditions List (ARCL): (184 conditions, Appendix G All Remaining Conditions List (ARCL))

    Conditions requiring reconciliation/discussion were dispositioned after thorough discussion inEL team working meetings to either:

    a. Other lists: ICL 1.0 v1, PFCL, RCL (all conditions with a concurrence ranking of 3 or higher were dispositioned to one of these lists).

    b. ARCL – Remaining conditions not otherwise dispositioned to the aforementioned lists comprise the ARCL. The ARCL was reviewed by SMEs to ensure there was no exclusion of a low-

concurrence but high-importance to exploration spaceflight condition. (Conditions on the ARCL have a concurrence ranking of ≤ 2).

2. Removed Conditions List (RCL): (66 conditions, Appendix F)
    a. Duplicate conditions were removed.
    b. Non-specific conditions that limited ability to identify supporting medical literature,obtain incidence data, assign medical resources, and/or assign associated Task Impairment values were removed (e.g., “non-specific musculoskeletal pain”).
    c. All conditions that were already accounted for in the ICL 1.0 v1 via combination (e.g., shoulder, elbow, and wrist sprain/strain were moved to the RCL as they are encompassed in the ICL 1.0 v1 condition “Upper Extremity Sprains/Strains”).
    d. All removed conditions were tracked and the reason for removal was recorded.
3. Proposed Future Conditions List (PFCL): (92 conditions, Appendix E). Any of the following criteria:
    a. Conditions that were deemed possible to occur in spaceflight and were considered relevant for exploration missions but did not merit ranking in the top 120 conditions based on lack of historic occurrence in spaceflight, low concurrence rating, and/or ELteam SME consensus, were deferred to the PFCL.
    b. Conditions that EL team SMEs felt were unlikely to occur in space due to the ability to mitigate the risk through engineering controls were deferred (e.g., Electrical Injury, as electrocution would require 2 layers of system failure in current vehicles, or by established standards for future vehicles).
    c. These conditions, and the reason they were deferred, were recorded in the PFCL for future iterations of IMPACT condition lists.
4. ICL 1.0 v1: (120 Conditions, Appendix C)

    As conditions were combined or split, they were moved to the ICL 1.0 v1. This list was reviewed in its entirety by EL team and best/worst-case scenario definitions were updated by SME consensus for every condition. When the ICL 1.0 reached 117 conditions, EL Team SMEs again reviewed the full list to assess whether:

    a. Any existing conditions should be deferred to the PFCL
        i. Two conditions were moved from the ICL 1.0 v1 to the PFCL as a result:
            1. Dental Caries – based on spaceflight operational dentist SME inputand EL team consensus.
            2. Ovarian Cyst – based on EL team SME consensus.
    b. Whether there were conditions missing from ICL 1.0 (regardless of whether theyexisted on the other lists (PFCL, RCL, ARCL)).

    This left 5 remaining slots for conditions on the ICL 1.0 v1 to reach the initial goal of 120 conditions. Twelve candidate conditions to fill the remaining 5 condition slots on the ICL 1.0 v1 were selected from the PFCL by the EL team. (Each SME reviewed the PFCL and proposed candidates. All proposed candidates were considered). Of these twelve, the final five conditions were identified by majority vote by the EL team.

CONDITIONS NOT EXPLICITLY STATED (CNES)

It should be noted that some conditions on ICL 1.0 v1 do not explicitly state that a condition is included in their title, but the best and worst-case scenario definitions encompass a spectrum of disease progression that includes another condition (e.g., “transient ischemic attack” is included in the best-case scenario for the condition “cerebral vascular

accident.") These conditions were tracked and are included in each CLiFF under the heading "Conditions Included, But Not Explicitly Stated (CNES)."

After its completion, three SMEs reviewed the ICL 1.0 v1 and provided comments regarding the best and worst-case scenarios,which were incorporated into the definitions. These SMEs were an astronaut physician and two operational flight surgeons.

ICL 1.0 VERSION CHANGES

During the process of evidence collection, the ICL 1.0 v1 was modified. In version 2 "ICL120 – Vertebral Disc Disorder" was removed and "ICL121 – BHP-Spaceflight Related Relationship Problems" was added. In version 3, "ICL27 – Cold Injury – Chilblains/Frostbite" and "ICL69 – Hypothermia" were removed. "ICL122 – Gravity Well - Entry Motion Sickness" and "ICL123 – Pregnancy, First Trimester" were added to version 3. In version 3.1, ICL 36 "Lunar Dust Exposure" was divided into ICL 36a and ICL 36b. For version 3.2, ICL 121 "BHP-Spaceflight Related Relationship Problems" and ICL 79 "Reactive Airway Disease" were deleted. The net effect resulted in a total of 119 conditions in the current ICL 1.0 v3.2. Condition additions, removals, and their rationale are detailed in TABLE 2. Notably, because the ICL 1.0 v1 condition names had already been configuration-managed, these changes did not result in alphabetization or renumbering the ICL 1.0 v3.2. Thus, after the removal of ICL27, ICL69, ICL79, ICL120, and ICL 121 there are no longer ICL27, ICL69, ICL 79, ICL120, or ICL 121 on the ICL 1.0 v3.2 as these condition numbers were retained by the removed conditions.

TABLE 2 ICL 1.0 VERSION 1.0 to 3.2 - CONDITION ADDITION AND REMOVAL RATIONALE

CONDITION	ACTION	RATIONALE
ICL27 - Cold Injury - Chilblains/Frostbite	Removed	After extensive discussion with engineering and ExMC Leadership, this condition was removed because: 1) There is not enough available information to generate incidence, 2) The risk of cold injury is dependent on mission phase, 3) Operational solutions/workarounds to mitigate the risk for cold injury are significant, 4) Any failures that resulted in cold injury would likely result in loss of the crew.
ICL 36a and 36b – Lunar Dust Exposure	Split into two conditions	ICL 36 Lunar Dust Exposure was divided into two conditions, based on the crewmembers' role. Crewmembers performing lunar surface EVAs have a 100% probability of lunar dust exposure while crewmembers inside the lunar habitat were determined to have a 75% probability of exposure to dust brought back by returning EVA crewmembers. In order to accommodate calculations in MEDPRAT, this split was necessary for v3.2.
ICL69 - Hypothermia	Removed	After extensive discussion with engineering and ExMC Leadership, this condition was removed because: 1) There is not enough available information to generate incidence, 2) The risk of hypothermia is dependent on mission phase, 3) Operational solutions/workarounds to mitigate the risk for hypothermia are significant, 4) Any failures that resulted in hypothermia would likely result in loss of the crew.

CONDITION	ACTION	RATIONALE
ICL 79 – Reactive Airway Disease	Removed	A review of possible overlapping conditions found that reactive airway disease as defined (a reaction after inhalation of a noxious substance) is already covered in other conditions. These include toxic inhalation, toxic inhalation of combustion products, and allergic reaction. Thus, it was removed for v3.2.
ICL120 - Vertebral Disc Disorder	Removed	The best-case and worst-case scenario definitions in this condition were vague, limiting the utility of literature searches. Further, and more importantly, all published cases of in-flight back pain during US Spaceflight were captured in other conditions (ICL101 - Sprain/Strain - Back, and ICL91 - Space Adaptation - Back Pain). Therefore, there is no added value of including this condition in the ICL 1.0.
ICL121 - BHP-Spaceflight Related Relationship Problems	Added and then removed	This condition narrowly missed being included in ICL 1.0 v1. When Vertebral Disc Disorder was removed, it was determined with ExMC leadership that this condition would be added since it was highly desired by BHP and the next condition in line for the list. Thus, it was added to ICL 1.0 v3. However, further review by psychiatry SMEs determined that this was not a true medical condition as it does not appear in DSM-5. It was removed for v3.2.
ICL122 - Gravity Well - Entry Motion Sickness	Added	ICL61 formerly included this condition (it was initially a Category 1/Category 2 rather than Best-Case/Worst-Case scenario condition). During the editor review process, it was determined that it was not possible to combine entry motion sickness and neurovestibular disturbance into one condition. Thus, the conditions were split as follows for ICL 1.0 v3: ICL61 Gravity Well - Neurovestibular Disturbance, and ICL122 - Gravity Well - Entry Motion Sickness. The best and worst- case scenario definitions for ICL122 were driven by available literature.
ICL123 - Pregnancy, First Trimester	Added	ICL 1.0 v1 included only ICL76 - Pregnancy, Risk For. The Proposed Future Conditions List (PFCL) contained a variety of pregnancy related conditions. The EL Team felt strongly that in addition to the risk of becoming pregnant, pregnancy itself should be a condition included on the ICL 1.0 and that this would address several of the PFCL conditions. ExMC leadership agreed, thus First Trimester Pregnancy was added to the ICL 1.0 v3.

BHP = Behavioral Health and Performance,
EL = Evidence Library,
ExMC = Exploration Medical Capability Element,
ICL 1.0 = IMPACT 1.0 Medical Conditions List.

3.1.3 Condition Definition

Conditions are defined and bound for modeling purposes using "best-case" and "worst-case" scenarios based on existing iMED architecture. These definitions are based on current medical literature and reflect best practice for determining incidence, differences in outcomes, and the capabilities and resources needed to treat each condition. This tailoring makes the condition definitions unique, requiring EL data consumers to understand the definition and the best-case/worst-case stratification to interpret all data associated with that condition. The condition definition process was conducted by the EL team with input from various specialists (Section 3.1.2.1). For example, the Human Systems Risk Board risk custodians for the Lunar dust risk were consulted to assist with formulation of the best-case and worst-case scenario definitions for ICL36A and ICL 36B – Dust Exposure - Lunar. The best-case scenario was defined as: "Lunar dust causing transient symptoms in the eyes, skin and respiratory tract that respond to conservative management." The worst-case scenario was defined as: "Lunar dust exposure that leads to sustained pulmonary symptoms requiring greater than 1 week of treatment."

Best-case scenario definitions are expected to resolve spontaneously or lead to optimal recovery for a given condition with minimal treatment. Worst-case scenario definitions respond poorly to initial treatment, require complex intervention, lead to a prolonged or incomplete recovery, and/or result in mortality despite use of the best available interventions.

A few conditions did not lend themselves well to this binary notation. Some such conditions were assigned a single definition with no corresponding best or worst-case (e.g., ICL85 – Shock, Cardiogenic). For others, such as ICL42 - EVA Related Hand Injury, the EL team determined the definitions should reflect two distinct categories of medical condition, with neither being valued as better or worse than the other, (i.e., "Category 1" and "Category 2" rather than "best-case" and "worst-case") based on incidence groupings and/or capability/resource requirements.

All changes to condition definitions in the ICL 1.0 are recorded, along with the dates the changes were accomplished, in the current v3.2.

The IMPACT tool suite uses these data to forecast a specified set of crew health and mission success risk metrics and to estimate what medical system design elements yield the lowest overall risk to the mission.

3.2 RAPID SYSTEMATIC REVIEW PROCESS

The EL team collected evidence for each medical condition via a rapid systematic review process, defined as 'a form of knowledge synthesis in which components of the systematic review process are simplified or omitted to produce information in a timely manner.'[8] Each condition required a unique search criteria and methodology, developed by the evidence-based medicine SMEs in consultation with appropriate clinical SMEs.

Information was collected using selected databases (including PubMed®, Google Scholar™, DynaMed®, Cochrane Library©, NASA Technical Reports Server [NTRS], and Defense Technical Information Center [DTIC]), optimizing search efficiencies scoped to capture enough literature to accurately address desired data points. This review did not encompass a comprehensive search of all available literature due to project resource and time constraints, but rather was driven by SME leads for each condition, using clinical acumen to identify the most appropriate and relevant literature. SMEs focused first on spaceflight data. If spaceflight data was unavailable, then they focused on terrestrial gold standard clinical practice guidelines and/or literature specific to population, environmental, or clinical management characteristics that best compared remote, low-resource circumstances (e.g., polar environments) or deployed populations (e.g., military) to those that could be experienced during exploration spaceflight.

[8]Tricco, A.C., Antony, J., Zarin, W. *et al.* A scoping review of rapid review methods. *BMC Med* **13,** 224 (2015). https://doi.org/10.1186/s12916-015-0465-6

3.2.1 Partnership with the University of Colorado School of Medicine

ExMC entered into a partnership agreement with the University of Colorado School of Medicine (CUSOM) to expedite evidence data collection. CUSOM offered three, 1-month electives to senior medical students, taught by clinical faculty at CUSOM, supported by ExMC clinical scientists and visiting lecturers with an expertise in space medicine. Following introductory lectures regarding the EL, biostatistics, epidemiology, and evidence-based literature searches, students were assigned ICL 1.0 conditions. They were closely precepted by library scientists, evidence-based medicine (EBM) biostatisticians, epidemiologists, and clinical faculty while obtaining spaceflight, analog, and terrestrial incidence, calculating best-case and worst-case probability, as well as using evidence to inform clinical phase 2 duration and outcome measures (RTDC and LOCL). In addition to standardized evidence collection, students completed a rough draft of the CLiFF. This student-draft was reviewed by clinical preceptors, then delivered to ExMC for review by a physician editor with NASA biostatistician input. Finally, the CLiFF was passed to the EL Project Scientist or another ExMC Clinical and Science Team physician for peer review. Ultimately, the evidence informing each CLiFF was determined by ExMC EL SME editors and finalized with the agreement of the Peer Reviewer/EL Project Scientist Lead.

The CUSOM partnership obtained the data informing the evidence for 84 of the 120 CLiFFs. ExMC internally sourced evidence for the remaining 36 conditions that were determined to require EL clinician expertise from the onset of the CLiFF building process because they required access to sensitive data, were more complex, or were spaceflight specific. The CLiFFs that were created entirely by ExMC EL Clinicians are shown in TABLE 3.

TABLE 3 CLiFF CONDITIONS CREATED ENTIRELY BY ExMC EL CLINICIANS

Condition Number	Condition Name
ICL4	ACUTE RADIATION SYNDROME
ICL6	ALTITUDE SICKNESS
ICL13	BHP – ADJUSTMENT DISORDER
ICL14	BHP – ANXIETY
ICL15	BHP – DEPRESSION
ICL16	BHP – GRIEF REACTION
ICL17	BHP – PSYCHOSIS SECONDARY TO DEPRESSION
ICL18	BHP – SLEEP DISTURBANCE
ICL21	BURN – MILD, THERMAL
ICL22	BURN – MODERATE TO SEVERE, THERMAL
ICL36	DUST EXPOSURE – LUNAR
ICL39	EVA RELATED DECOMPRESSION SICKNESS
ICL40	EVA RELATED DEHYDRATION
ICL41	EVA RELATED FINGERNAIL DELAMINATION
ICL42	EVA RELATED HAND INJURY
ICL43	EVA RELATED HEAT ILLNESS
ICL44	EVA RELATED PARESTHESIA
ICL45	EVA RELATED SHOULDER INJURY
ICL46	EVA RELATED SUIT CONTACT INJURY
ICL56	FRACTURE – WRIST
ICL58	GASTRITIS/REFLUX/ESOPHAGITIS
ICL59	GASTROENTERITIS/ACUTE DIARRHEA
ICL61	GRAVITY WELL – NEUROVESTIBULAR DISTURBANCE
ICL69	HYPOTHERMIA
ICL76	PREGNANCY, RISK FOR
ICL81	RESPIRATORY TRACT INFECTION – LOWER
ICL82	RESPIRATORY TRACT INFECTION – UPPER
ICL88	SKIN INFECTION - VIRAL/FUNGAL
ICL95	SPACE ADAPTATION – INSOMNIA

Condition Number	Condition Name
ICL98	SPACE ADAPTATION – URINARY RETENTION
ICL99	SPACE ADAPTATION – URINARY INCONTINENCE
ICL100	SPACE FLIGHT ASSOCIATED NEURO-OCULAR SYNDROME (SANS)
ICL109	TOXIC DERMAL EXPOSURE
ICL121	BHP – SPACEFLIGHT RELATED RELATIONSHIP PROBLEMS
ICL122	GRAVITY WELL – ENTRY MOTION SICKNESS
ICL123	PREGNANCY, FIRST TRIMESTER

3.2.2 Evidence Collection Workflow and Versioning to Complete CLiFFs

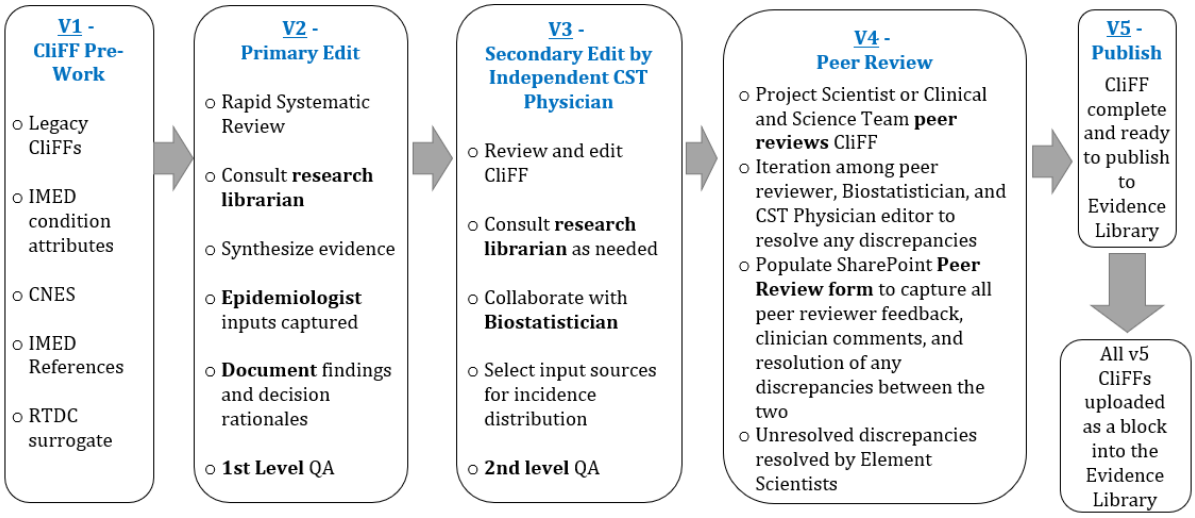


Figure 3 CLiFF Development Versions

The following is a summary of the versioning (Figure) and workflow (Figure) used to create a CLiFF. For all CLiFFs, ExMC EL SMEs completed pre-work before evidence searches began in which they identified legacy IMM CLiFFs and associated references that could inform the update, reviewed the ICL 1.0 condition definition, reviewed associated CNES (Section 3.1.2.5), and identified appropriate RTDC surrogates. In some cases, EL SMEs determined that RTDC was 100% for either the best- or worst-case scenario and that a literature search for evidence informing RTDC was not required. In such cases, the RTDC value was assigned at this time. This version of the CLiFF was denoted version 1.

Version 1 of the CLiFF was then passed to either the CUSOM or an ExMC clinician editor for rapid systematic review. Spaceflight, analog, and terrestrial incidence, best-case/worst-case probability, clinical phase 2 duration, RTDC, and LOCL data were collected with notes explaining where the data came from and rationale for its inclusion. This was denoted as version 2 of the CLiFF.

The 84 conditions for which CUSOM completed version 2 were then passed back to ExMC clinicians for editing. The conditions that underwent rapid systematic review internally were edited by the same ExMC EL clinician who performed the systematic review. Using a comprehensive checklist, EL SME clinicians edited the CLiFFs by critically reviewing the evidence collected. The editor determined the best evidence to inform the incidence and confirmed this with the peer reviewer (Section Partnership with the University of Colorado School of Medicine) at this point. With agreement from the peer reviewer, the editor sent the evidence to biostatistics for creation of an incidence distribution. The editor then critically reviewed the evidence driving best and worst-case scenario

probabilities and assigned these appropriately. The duration, RTDC, and LOCL data were likewise reviewed by the editor and assigned in the CLiFF. All prose in the CLiFF was updated in accordance with any changes that were made. This draft of the CLiFF was denoted version 3.

Version 3 was passed to the ExMC Peer Reviewer (either the Evidence Library Project Scientist or another ExMC Clinical and Science Team Physician). The peer reviewer completed a comprehensive review of the CLiFF and any discrepancies were resolved between the editor and the peer reviewer at this stage. If necessary, Element Scientists were consulted. Peer reviewers completed a Peer Review form that underwent configuration management for each CLiFF. This draft of the CLiFF was denoted version 4.

Version 4 of the CLiFF was passed to the EL Team Lead for spell checking, formatting, and configuration management. This draft was denoted version 5. Version 5, the finished CLiFF, was delivered to IMPACT.

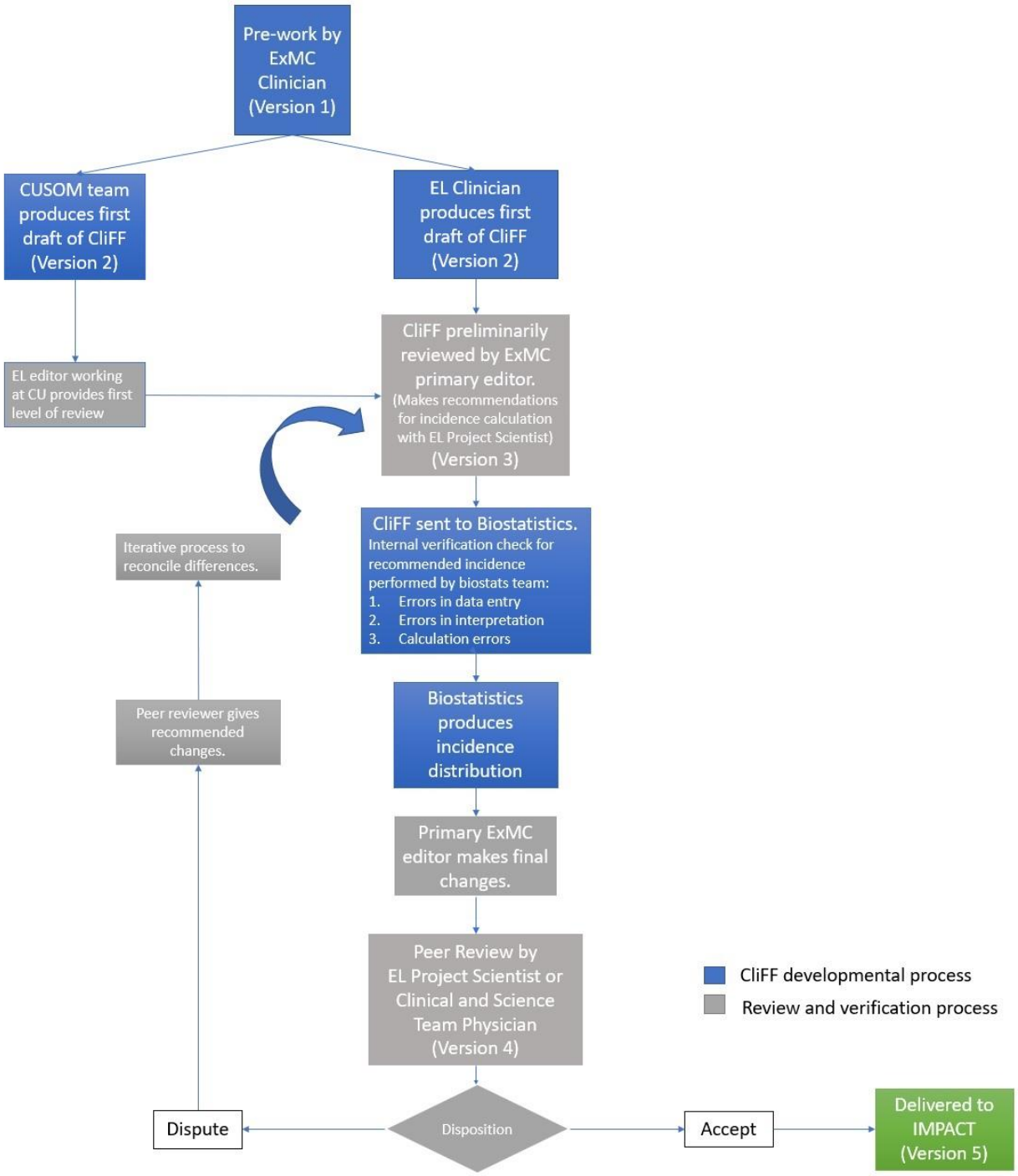


Figure 4 CLiFF Development Workflow

3.2.3 Evidence Library Data Sources

The specific source databases and inputs informing the EL varied according to EBM rapid systematic review best practices. They were defined by EL team members in consultation with experts in terrestrial evidence-based medicine and library science. Strategic partners at CUSOM: Strauss Health Sciences Library, as well as clinical faculty with expertise in biostatistics and evidence-based medicine, provided EL team members access to library and subscription-based data sources listed below, library services to locate key publications, and SME support for the building and documentation of searches. The following sources were considered for use for all conditions.

3.2.3.1 PubMed®

Each condition-specific incidence search performed by CUSOM and some treatment and outcome searches began with a PubMed®[9] database search via identifying Medical Subject Heading (MeSH) terms relevant to the specific condition. These searches were initially built by medical students with library science and biostatistical mentorship, but this process evolved to have the library scientists themselves create the actual search builders—which proved to be both more efficient and more accurate. Searches were augmented with synonyms for the medical condition (e.g., 'allergic reaction' and 'hypersensitivity reaction') and organized into the appropriate syntax for the PubMed® database. Once the base search was completed, filter searches such as "Space Medicine" or "incidence" or criteria such as "human only" or "adult" were applied to narrow results.

3.2.3.2 Google Scholar™

Google Scholar™[10] is an alternative search engine to PubMed® and ranks documents by weighing an algorithm of the full text of each document, source journal, authorship, as well as quantity and dates of citations in peer review. MeSH terms used to inform PubMed® were also used when searching via Google Scholar™.

3.2.3.3 DynaMed®

DynaMed®[11] is an electronic evidence-based, primary care database designed to provide point-of-care health information to clinicians in active practice. This database is frequently updated and represents broad terrestrial research and common clinical guidance. The EL team used DynaMed® to supplement searches for incidence, treatment, and outcome data. Limitations in the use of DynaMed® include the lack of tailoring of medical evidence or clinical guidance to the unique population, environment, and medical resources available in an exploration spaceflight setting.

3.2.3.4 Cochrane Library©

The Cochrane Library©[12] is a collection of databases containing different types of high quality, independent evidence to inform healthcare decision making. These databases are frequently updated and represent broad terrestrial research and common clinical guidance. The Cochrane Library© was included to supplement treatment and outcome data when necessary—especially searches for "untreated" scenarios.

[9]PubMed [Internet]. Bethesda (MD): National Library of Medicine (US). [1946] Available from: https://www.ncbi.nlm.nih.gov/pubmed/
[10] Google Scholar. https://scholar.google.com/
[11]DynaMed [Internet]. Ipswich (MA); EBSCO Information Services. 1995- [cited 2021 Jan]. Available from http://www.www.dynamed.com.Registration and login required.
[12]Cochrane Library [Internet]. London (UK); John Wiley & Sons, Inc. [cited 2021 Jan]. Available from: https://www.cochrane.org

3.2.3.5 Other Data Sources

Space medicine and analog specific searches utilized the Defense Technical Information Center,[13] the repository for research and engineering information for the United States Department of Defense; the NASA Technical Reports Server,[14] which provides access to NASA metadata records, full-text online documents, images, and videos including scientific and technical information created or funded by NASA; and Barratt, Baker, & Pool's *Principles of Clinical Medicine for Space Flight*,[15] the premiere text repository of clinical space medicine. Data from searches were supplemented with published data from the Lifetime Surveillance of Astronaut Health (LSAH)[16] occupational surveillance program, LSAH data used for IMM, available reports of in-flight medical events, and legacy IMM CLiFFs.

3.2.3.6 ExMC Generated CLiFF Data Sources and Methodology

ExMC generated CLiFFs for 36 conditions (TABLE 3). These conditions were researched by ExMC without the assistance of the CUSOM students because of their specific spaceflight nature. In such instances, the search methodology detailed in the following section did not apply (e.g., there was no utility to performing searches for terrestrial data for Space Adaptation Syndrome conditions). In these instances, ExMC editors were given the freedom to find applicable evidence from whatever source they felt appropriate. Much of this evidence was sourced from the NASA Technical Reports Server. In some instances, it was supplemented with data from the sources already outlined or used the methodology in Section 3.2.4.

3.2.4 Search Methodology

Time and resource constraints did not permit a full systematic review and meta-analysis for each of the 120 conditions. As such, the EL team elected for a rapid systematic review process combining evidence from high-quality summary databases, medical literature databases, and sources of spaceflight medical event data. This methodology was used for the 84 condition CLiFFs that the CUSOM students generated. The review process sought the following information:

- Condition incidence.
- The probability of the best *vs.* the worst-case scenario of the condition.
- Outcome measures for mortality and morbidity; treated and untreated, for both best and worst-case scenarios.
- Condition incidence for return to definitive care, based on a pre-determined surrogate [e.g., hospitalization; need for surgery; or other critical procedure]: treated and untreated, for both best and worst-case scenarios.
- Duration of clinical phase 2 (i.e., treatment or convalescence, prior to a clinical end-state) treated and untreated, for both best and worst-case scenarios.

Inclusion/exclusion criteria were highly condition-specific but, in general, limited to adult studies (age younger than 70 years) with no or well-controlled minor medical conditions (e.g., hypertension, hyperlipidemia). An example search term matrix is included in TABLE 4.

[13]Defense Technical Information Center. Fort Belvoir (VA). US Department of Defense. [cited 2021 Jan]. Available from: https://discover.dtic.mil/
[14]NASA Technical Reports Server. National Aeronautics and Space Administration. [cited 2021 Jan]. Available from: https://ntrs.nasa.gov/
[15]Barratt. M., Baker, E., & Pool, S. (2019) Principles of clinical medicine for spaceflight. V2. Springer.
[16]LSAH home. (n.d.). Retrieved February 1, 2021, from https://lsda.jsc.nasa.gov/LSAH/LSAH_Home.

TABLE 4 EXAMPLE SEARCH STRATEGY FOR ICL7 - ANAPHYLAXIS

MEDLINE (VIA PUBMED®)				
SEARCH DATE =	**1946 TO PRESENT**			
SEARCH #	**SEARCH STRATEGY**	**HARVESTED TERMS**	**DATABASE FORMAT**	**# OF RESULTS**
#1	Anaphylaxis [Mesh]	Anaphylaxis	[Mesh]	21035
#2	Anaphylactoid Reaction[tw]	Anaphylactoid Reaction	[tw]	876
#3	Anaphylactoid Reactions[tw]	Anaphylactoid Reactions	[tw]	1076
#4	Anaphylactic Reaction[tw]	Anaphylactic Reaction	[tw]	2532
#5	Anaphylactic Reactions[tw]	Anaphylactic Reactions	[tw]	2575
#6	Anaphylactic Shock[tw]	Anaphylactic Shock	[tw]	3595
#7	Anaphylactoid Shock[tw]	Anaphylactoid Shock	[tw]	131
#8	Anaphylactoid Shocks[tw]	Anaphylactoid Shocks	[tw]	7
#9	Anaphylaxis[tw]	Anaphylaxis	[tw]	30357
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9			33227
#11	Aerospace Medicine[Mesh] OR space medicine[tw] OR Aerospace Medicine[tw] OR Space Flight[Mesh] OR Space Flights[tw] OR Spaceflight[tw] OR Spaceflights[tw] OR Space Flight[tw] OR Space Travel[tw] OR Space Travels[tw] OR Space Exploration[tw] OR Space Explorations[tw] OR Space Walk[tw] OR Space-Walks[tw] OR Extravehicular Activity[tw] OR Extravehicular Activities[tw] OR Spacecraft[tw] OR Spacecrafts[tw]OR Space Ship[tw] OR Space Ships[tw] OR Space Vehicles[tw] OR Space Vehicle[tw] OR Spaceship[tw] OR Spaceships[tw] OR Space Vehicles[tw] OR Space Vehicle[tw] OR Spaceship[tw] OR Spaceships[tw] OR Space Shuttle[tw] OR Space Shuttles[tw] OR Space Capsule[tw] OR Space Capsules[tw] OR Extraterrestrial Environment[Mesh] OR Extraterrestrial Environments[tw] OR ExtraterrestrialEnvironment[tw] OR Weightlessness[Mesh] OR ZeroGravity[tw] OR Microgravity[tw] OR Weightlessness[tw] OR Astronauts[Mesh] OR Astronauts[tw] OR Astronaut[tw] OR Cosmonauts[tw] OR Cosmonaut[tw] OR Space Simulation[Mesh] OR Space Simulation[tw] OR Space Simulations[tw] OR Orbital Simulation[tw] OR Orbital Simulations[tw] OR Space Model[tw] ORSpace			43701

MEDLINE (VIA PUBMED®)				
SEARCH DATE =	**1946 TO PRESENT**			
SEARCH #	**SEARCH STRATEGY**	**HARVESTED TERMS**	**DATABASE FORMAT**	**# OF RESULTS**
	Models[tw] OR Apollo [tw] OR sputnik[tw] OR Biosputnik[tw] OR Soyuz[tw] OR Soiuz[tw] OR Salyut[tw] OR saliut[tw] OR kosmos[tw] ORaragatz[tw]			
#12	#10 AND #11			12

Evidence-based medicine and library science SMEs at the CUSOM, in partnership with ExMC clinicians devised the following search algorithm for the EL incidence, treatment and outcome endpoints. The choices and search order of databases were determined by balancing the greatest likelihood of success in acquiring desired data, scaled across 120 medical conditions, with a need for search efficiency within the short timeframe of this project.

Included studies also fell into one of three broad categories:

- Data for medical conditions seen in terrestrial medicine (e.g., allergic reaction, appendicitis, etc.) were derived from population-based studies of a representative terrestrial population that matched anticipated astronaut demographics as closely as possible.
- Data for conditions related to spaceflight (e.g., space motion sickness) were drawn from available spaceflight data, published studies and case reports, and modeling predictions.
- Data for conditions related to injury/toxin exposure (e.g., smoke inhalation, etc.) and medical management of such events in austere and self-contained environments were drawn from analogous populations engaged in similar remote or limited activities (e.g., polar research stations and deep-sea research vessels), or spaceflight data. Additionally, models previously developed for spaceflight specific concerns (such as risk prediction of onboard fire or toxic atmosphere) were reviewed for applicability to modeling of future vehicles or DRMs. When possible, NASA engineering experts were consulted to better characterize risk parameters (toxic smoke inhalation, partial pressure of oxygen, temperature exposures, etc.).

Searches were reviewed by EL SMEs for inclusion/exclusion criteria relevant to the specific condition. Lists of articles informing condition incidence and outcomes were subsequently generated from which relevant data were drawn to synthesize the final CLiFF values. If editors felt that supplemental resources not included in these lists were critical to the CLiFF, they were added during the editing process.

TABLE 5 DATA SOURCE AND SEARCH ORDER

EL Data Required	Data Source and Priority Search Order
Incidence - Space & Analog environments	1. PubMed® 2. Google Scholar™ 3. NASA Technical Reports Server 4. Textbook: Barratt, Baker & Pool, eds. *Principles of Clinical Medicine for Spaceflight*. 2019 5. Defense Technical Information Center (DTIC) 6. Previous CLiFF citations (IMM) 7. LSAH data 8. Models 9. System Probabilistic Risk Assessments (PRAs)
Incidence - Terrestrial	1. DynaMed®* 2. PubMed® 3. Google Scholar™
Probability of Best vs. Worst-Case Scenario	1. PubMed® 2. Google Scholar™ 3. NASA Technical Reports Server 4. Textbook: Barratt, Baker & Pool, eds. *Principles of Clinical Medicine for Spaceflight*. 2019 5. Defense Technical Information Center (DTIC) 6. Previous CLiFF citations (IMM)
Duration - Treated Best-case & Treated Worst-case	1. DynaMed®* 2. Cochrane Library©
RTDC - Treated Best-case, Treated Worst-case LOCL - Treated Best-case, Treated Worst-case	1. DynaMed®* 2. PubMed® 3. Google Scholar™
Duration - Untreated Best-case, Untreated Worst-case RTDC - Untreated Best-case, Untreated Worst-case LOCL - Untreated Best-case, Untreated Worst-case	1. PubMed® 2. Google Scholar™
(*) indicates a search process terminated at the DynaMed® database, if desired data was acquired in that particular search	

3.2.5 Documentation of Review Process

Specifics on each condition's literature search were recorded in a comprehensive Microsoft Excel™[17] file CLiFF workbook, including databases searched, search terms used, results, and notes. Relevant articles from the individual data point searches (e.g., treated best-case RTDC) were cached in a commercial reference management software application (EndNote™). The number of relevant articles imported into the reference management software was recorded in the workbook. For each article reviewed, specific inclusion/exclusion criteria regarding data ultimately incorporated into IMPACT were clarified in a table adjacent to the search results. For the data points used, population information from the article such as age, sex, health status, and pre-existing conditions of the population was likewise documented in the search table. An example of the final CLiFF documentation template is shown in Appendix B Examples (ICL35 and ICL97) of Clinical Data for Import into IMPACT-MD (CLiFF Tab 9B).

3.3 EVIDENCE LIBRARY PEER REVIEW

Each condition's medical evidence was independently reviewed and agreed upon by at least two ExMC-associated clinicians prior to delivery to IMPACT-MD. Condition-specific medical evidence subject to peer review included all data contained in the corresponding CLiFF, its EndNote™ folder, and the associated CRT. Peer reviewers were either the EL Project Scientist or another Clinical and Science Team physician. The peer-reviewing clinician was not involved in the rapid systematic review process for assigned conditions to limit bias. The reviewer was provided with a configuration managed version of the data products and used a Microsoft SharePoint©[18] site form to provide feedback to the condition editor (Appendix I CLiFF Peer Review Form). If necessary, ExMC condition editors modified the configuration managed versions of the data products based on the peer reviewer feedback. In the event of conflicts of opinion between the Clinical and Science Team reviewer and editor, the EL Project Scientist acted as an unbiased third party to make a final decision. When the EL Project Scientist was the peer reviewer, the ExMC Element Scientist acted as the third party. Project tempo and schedule limitations required iteration between peer reviewer and editor to be completed within a narrow time window. The results of the peer review were documented and archived as part of the configuration management process. Peer reviews by clinicians outside of ExMC or NASA were outside the scope of the IMPACT 1.0 effort but may be considered for future iterations of the Evidence Library. Peer review processes for data after import into the IMPACT-MD are beyond the scope of this document.

3.3.1 Condition Incidence Collection, IMPACT Condition Groupings, Crew Characteristics, and Data Sources

3.3.2 Condition Incidence Collection Overview

Within each CLiFF, and in IMPACT-MD, incidence of each condition is represented as either an incidence rate or an incidence proportion.

Incidence rates (IRs) were assessed for conditions that may repeatedly occur throughout the mission or during a given mission phase (i.e., deep space transit, surface operations). IRs are selected to inform the modeling of conditions where the number of new medical events occurring in the spaceflight environment are primarily a function of how much time has elapsed. The current model assumes constant incidence rates over the duration of the segment (Poisson occurrence distribution). The highest value data for informing incidence rate distributions are the total events which have occurred among crew and the total time crew are at risk. In situations in which these data were available, the expected IR was then directly calculable (i.e., events/person-years). Appropriate distributions defining rates include Gamma, log-normal, and fixed rates. Distribution parameters were most often estimated through Bayesian analysis of relevant source data under uninformative priors. Most ICL 1.0 conditions were represented with IRs.

[17]Microsoft Excel. https://www.microsoft.com/en-us/microsoft-365/excel
[18]Microsoft Sharepoint. https://www.microsoft.com/en-us/microsoft-365/sharepoint/collaboration

Incidence proportions (IPs) were assessed for conditions for which the crew is at risk during specifically defined time intervals (generally brief) as a yes/no occurrence (Binomial occurrence distribution) associated with singular events, rather than throughout the mission. These included conditions associated with gravity-well transitions, with environmental exposures, EVAs, and some longer-duration spaceflight exposures (e.g., Spaceflight-Associated Neuro-ocular Syndrome [SANS]). Distributions for IPs are best informed by the total events occurring among crew and the total number of crew at risk. The expected IP is then calculable (i.e., events/person-at-risk). Appropriate distributions defining proportions include beta or fixed. Distribution parameters were most often estimated through Bayesian analysis of relevant source data under uninformative priors. Examples of conditions represented with IPs include space adaptation back pain, space motion sickness, and decompression sickness secondary to EVA.

3.3.2.1 Incidence Distributions

As above, for describing incidence, all conditions were modeled through 2 possible incidence mechanisms – as conditions that occur over time at a constant rate (incidence rates), or as yes/no events (incidence proportions) tied to EVA activities, environmental exposures, space adaptation, or gravity well transitions. Depending on whether the condition was modeled through a rate or proportion, certain possible distributions could be specified. The following, TABLE 6, shows appropriate distributional choices for each, as well as the parameters used to define them. Further, formulas for calculating summary statistics (mean and standard deviation) of the distribution are included.

TABLE 6 STATISTICAL DISTRIBUTION PARAMETERS

Occurrence Distribution	Appropriate Incidence Distributions	Statistical Parameters	Distribution Mean	Distribution Standard Deviation
Poisson (rates per person-year))	Gamma	shape, rate	shape/rate	sqrt (shape / rate^2)
	log-normal	Mean, Standard Deviation	Mean	Standard Deviation
	Fixed rate	IR	IR	NA
Binomial (proportions per person-event)	Beta	alpha, beta	alpha/(alpha+beta)	sqrt((alpha * beta) / ((alpha + beta)^2 * (alpha + beta +1)))
	Fixed proportion	IP	IP	NA

Some of these distributions are only associated with certain types of evidence. For example, the bone fracture model created by the Glenn Research Center (GRC), used to inform the incidence of ICL56 – Fracture, Wrist and ICL 54 – Fracture, Femur, uses a log-normal distribution. For Probabilistic Risk Assessment (PRA) models that did not come with uncertainty metrics, fixed constants were assumed. However, most conditions were modeled through Bayesian analysis of source reference data and resulted in either a Gamma distribution for rates, or a Beta distribution for proportions.

3.3.2.2 Incidence Distribution Development Process

The overall Biostatistics workflow for completing distributions was the following for each condition:

Information received – Clinicians determined the most clinically relevant source(s) for data to define incidence distributions.

1. Distribution developed – Biostatistician analyzed the evidence and developed the incidence distribution. This process was recorded in the Incidence Distribution Document created by the Biostatistician for each CLiFF.

2. Analysis verified – A second statistician verified any analysis, the approach used, and reporting steps within the Incidence Distribution document.

3. Results communicated and accepted– The Incidence Distribution Document was reviewed by the editing clinician prior to use in the CLiFF. This document was summarized in the Overall Incidence Summary in the CLiFF. The Incidence Distribution Document was then provided to the Clinical and Science Team Lead for configuration management.

Sometimes, further peer review by the clinical team would restart this process. A change in the most clinically relevant sources would lead to revisions. Revision Incidence Distribution documents, created by the biostatistician, were denoted by version in the document title and contained corresponding notes related to any updates.

3.3.2.3 Evidence Data

As mentioned above, most conditions were analyzed through Bayesian analysis of data obtained from one or more reference sources. The optimal data for defining models were events and person-years for rates and events and persons-at-risk for proportions. Sometimes these quantities needed to be estimated through census data, or through the reported means and uncertainty (either standard deviations, or confidence limits). Whenever quantities were estimated, the sources and methods were documented in the Incidence Distribution Document.

3.3.2.4 Bayesian Models

Bayesian models were developed to define the posterior incidence distributions.

For rates, the models were defined as follows:

- For each study *i*, $events_i \sim Poisson(\lambda * followup_i)$ where events denotes the total number of cases from the study, and follow up denotes the total follow up time.

- Uninformative priors were set for the incidence rate, $\lambda \sim$ Gamma (shape=0.001, scale=0.001).

For proportions, the models were defined as follows:

- For each study *i*, $events_i \sim$ Binomial (n_i, p) where events denotes the total number of cases from the study, and n denotes the total persons-at-risk.

- Uninformative priors were set for the incidence proportion, $p \sim$ Beta(alpha=1, beta=1) – also known as the uniform (0,1) distribution.

Models were run within WinBUGS[19] (Bayesian inference Using Gibbs Sampling) to generate samples from the posterior distributions. Five thousand iterations after one thousand discarded samples were used for analysis. Simulation diagnostic plots were included in the Incidence Distribution documents. Posterior distribution estimates for the mean and standard deviation of the incidence parameter were used to identify the parameter estimates of each distribution by matching moments. Basically, by inverting the mean and standard deviation equations above the appropriate parameters needed to define the distribution could be determined.

[19]Lunn DJ, Thomas A, Best N, Speigelhalter D. (2000) WinBUGS – a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing, 10:325-337.

3.3.2.5 Other Conditions

As stated earlier, most GRC-produced models (wrist and hip fractures, nephrolithiasis, and gallstone disease) naturally come with log-normal distribution specifications which could be used directly without further analysis. Other conditions were modeled through probability calculations based on PRA model estimates. When uncertainty was included (e.g., confidence limits), distribution uncertainty was specified by matching. For example, confidence limit width was estimated to be 2x1.96xSD (the Normal approximation) to estimate an SD for the appropriate incidence distribution.

3.3.2.6 Incidence Data Selection

The possible sources of data that informed the incidence calculation included spaceflight, analog, terrestrial, modeling, and engineering analysis (such as PRA). Because the Bayesian analysis of relevant source data considered all subjects equally from any study used in the incidence calculation, it was important to ensure that only the data most relevant to spaceflight were used. For example, if there were informative studies that included both terrestrial investigations and spaceflight data, and there was reason to believe spaceflight incidence would differ, it was often necessary to consider only the spaceflight data. Terrestrial data may include studies that have an enormous number of subjects, making the uncertainty of the estimate very small. Spaceflight reports, on the other hand, usually have a small sample size which comes with large uncertainty in the rate estimate. Meta-analysis across studies is weighted by this uncertainty, making the influence of small samples on the incidence calculation negligible compared with a more precise estimate from a much larger data set. Consequently, spaceflight data, when available, was used exclusively if it was felt to reflect the spaceflight environment most accurately.

Spaceflight data were not used in situations where subject numbers were extremely small and possibly non-predictive or when the data originated from old vehicle or suit configurations that are no longer used. An example of this occurred with ICL119 – Venous Thromboembolism. Available spaceflight data found one, or possibly two, subjects out of 11 tested to have non-occlusive thrombi during spaceflight.[20] These data were not felt to be predictive of future incidence by the ExMC editor and peer reviewer; therefore, adjusted terrestrial data were used instead.

Modeling analysis was used when it closely matched a condition on the ICL 1.0. Modeling was needed when there was inadequate or incomplete spaceflight information available or when significant predictive analysis needed to be done (e.g., nephrolithiasis risk, fracture risk, fire risk). Engineering analyses such as PRAs could be problematic to use as they provided a general risk assessment but not the uncertainty estimates needed to develop an incidence distribution. However, in some cases PRA data were the only source of information available given that the medical condition occurs only when there is a system failure (e.g., overheating inside a spacesuit during EVA). In such cases, a fixed constant was often chosen to represent incidence.

3.3.2.7 IMPACT Condition Groupings

In addition to the clinical groupings outlined above, some conditions only occur under specific circumstances or at specific phases of the mission (e.g., space adaptation motion sickness, or fingernail delamination related to EVA). The grouping of specific conditions is labelled with “types” instructing MEDPRAT to treat these conditions according to further parameters defined by the EL team. These parameters define the statistical modeling framework for the specific conditions, (e.g., the number of occurrences and the duration of the special circumstances under which they occur). For example, space adaptation motion sickness only occurs during mission phases that include a transition from ground to space, (e.g., launch from Earth and launch from the lunar surface). The designation as a ‘SAS’ (Space Adaptation Syndrome) condition instructs MEDPRAT to utilize additional parameters defining the window of time after launch when this condition can occur and the incidence of the condition among crewmembers within that window. Two other “types” exist, ‘EVA’ and ‘Environmental.’

[20] Auñón-Chancellor SM, Pattarini JM, Moll S, Sargsyan A. Venous Thrombosis during Spaceflight. N Engl J Med. 2020 Jan 2;382(1):89-90. doi: 10.10 56/NEJMc1905875. PMID: 31893522.

Similar groupings, referred to as “modifiers,” existed in iMED for SAS, EVA, and solar particle event (SPE) exposures. For the EL update, additional groups were added to accommodate the expanded DRM and the term “modifier” was changed to “condition groupings” to avoid confusion with the statistical term “effect modifier.” SPE was broadened to reflect any environmental exposure.

EL condition groupings include:

A. Category I:
    1. Space Adaptation Syndrome (SAS)
    2. Gravity Well Transition (GWT)
    3. Lunar Surface Operations (LSO)
    4. Martian Surface Operations (MSO)

B. Category II:
    1. Space Extravehicular Activities (SEVA)
    2. Lunar Surface Extravehicular Activities (LEVA)
    3. Martian Surface Extravehicular Activities (MEVA)

C. Category III:
    1. Environmental (Env)

There are three categories for EL condition groupings and each category.

Category I conditions are represented as the 'SAS' type in MEDPRAT. When MEDPRAT progresses to the indicated time where SAS type events are possible, informed by EL parameters, incidence proportions are generated for each crewmember at risk. The outcome of a binomial trial, with probability parameter as incidence proportion, determines if the condition will occur or not within each crewmember. If a condition is found to occur, the timing of the condition is generated through a PERT distribution with parameters per condition defining the first occurrence time (minimum), most likely occurrence time (mode), and last occurrence time (maximum). Similarly, for the IP conditions described above, the incidence proportion distributions representing these conditions are best informed with observed condition occurrences and total number of events putting crewmembers at risk. The timing of these conditions within MEDPRAT incorporates expected durations of a given medical risk, or specific timeframes of the mission that encompass the duration of the risk. For example, SAS occurs only after the transition *from* a gravity well, such as an astronaut leaving the Earth or the Moon and transitioning *into* microgravity and ceases to be a risk after adaptation occurs (approximately 5 days).

Category II represents episodic events like space, Lunar, or Martian extravehicular activities (SEVA, LEVA, MEVA, respectively). Since these are discrete events, this category is best informed using the IP approach (number of conditions observed or anticipated to occur and the number of events putting the astronauts at risk). Category II conditions are represented as the 'EVA' type in MEDPRAT. Analogous to SAS, when EVAs are performed during the simulated mission, MEDPRAT generates the related condition's incidence proportion per EVA crew from the incidence proportion distribution and then uses a binomial draw to determine if each condition occurs or not, per EVA. If the condition is found to occur, onset is set as immediate (start of the EVA) and therefore no additional parameters are needed. The activity schedule (including EVA times) is included as a direct input into MEDPRAT. Some of the EVA condition incidence proportion distributions were based on predictions for an assumed 6-hour EVA length. However, duration of EVA within MEDPRAT does not play a role in this metric, only the EVA event itself. For those conditions assuming 6-hour EVA length, the incidence distribution document also contains an incidence rate distribution that could be utilized later to incorporate EVA length.

Category III contains all 'Environmental exposures,' which are associated with linked conditions in the current EL (e.g., SPE-related acute radiation sickness [ARS]). Category III conditions are represented as the 'Environmental' type in MEDPRAT. The exposure events themselves are generated based on incidence rates, and then incidence proportions define the probability that crew develop the condition given the exposure. Onset is immediate at the time of the environmental exposure. Current environmental exposures include SPE, smoke from combustion, other toxic inhalants, and lunar dust. During a simulation, once an environmental exposure event occurs, each crewmember is susceptible to developing the related condition. ARS occurring after an SPE is an example. The information for this grouping was derived from the IMM and relevant computational models.

TABLE 7 shows the EL condition groupings, their associated parameters, the source of this parameter data, and the specific conditions within each group. Each condition falls into only one category. These are EL groupings, not IMPACT groupings or types. Their purpose is to filter results according to the grouping of interest *after* an MEDPRAT run. As the team performs literature reviews in future versions, conditions may be added or removed from these groupings, based on consultation with project stakeholders. This document will be updated in the future to reflect these changes.

TABLE 7 IMPACT CONDITION GROUPINGS WITH CURRENT ASSOCIATED MODEL PARAMETERS AND SOURCES

	Category 1				Category 2			Category 3
Grouping	**SAS**	**Gravity Well Transition**	**Lunar Surface Operations**	**Martian Surface Operations**	**Space EVAs (SEVA)**	**Lunar Surface EVAs (LEVA)**	**Martian Surface EVAs (MEVA)**	**Environmental**
Model Parameters	**Distribution and associated parameters for incidence proportion distribution** **Incidence Type:** Fixed or Beta **Fixed.IP:** incidence proportion for fixed condition probability **Beta.alpha:** alpha parameter of beta distribution for condition probability **Beta.beta**: beta parameter of beta distribution for condition probability	**Distribution and associated parameters for incidence proportion distribution** **Beta.alpha:** alpha parameter of beta distribution for condition probability **Beta.beta**: beta parameter of beta distribution for condition probability **Occurrence RangeMin:** First observed occurrence of condition **Occurrence RangeMax:** Last observed	**Distribution and associated parameters for incidence. Can be either rate or proportion (for EVA-linked)**	**Distribution and associated parameters for incidence. Can be either rate or proportion (for EVA-linked)**	**Distribution and associated parameters for incidence proportion distribution** **Incidence Type:** Fixed or Beta **Fixed.IP:** incidence proportion for fixed condition probability **Beta.alpha:** alpha parameter of beta distribution for condition probability **Beta.beta**: beta parameter of beta distribution for condition probability	**Distribution and associated parameters for incidence proportion distribution** **Incidence Type:** Fixed or Beta **Fixed.IP:** incidence proportion for fixed condition probability **Beta.alpha:** alpha parameter of beta distribution for condition probability **Beta.beta**: beta parameter of beta distribution for condition probability	**Distribution and associated parameters for incidence proportion distribution** **Incidence Type:** Fixed or Beta **Fixed.IP:** incidence proportion for fixed condition probability **Beta.alpha:** alpha parameter of beta distribution for condition probability **Beta.beta**: beta parameter of beta distribution for condition probability	**Distribution and associated parameters for incidence of the exposure and associated condition. Exposure defined by rate condition defined by proportion given exposure** **Env.Incidence.Type:** Fixed (IR) or Gamma **Condition.Incidence.Type:** Fixed (IP) or Beta **Env.Fixed.IR:** incidence rate of environmental exposure **Env.Gamma.Shape:** shape parameter of gamma distribution for environmental incidence **Env.Gamma.Rate:** rate per year parameter of gamma distribution for environmental incidence **Fixed.IP:** incidence proportion for condition

	Category 1				Category 2			Category 3
Grouping	**SAS**	**Gravity Well Transition**	**Lunar Surface Operations**	**Martian Surface Operations**	**Space EVAs (SEVA)**	**Lunar Surface EVAs (LEVA)**	**Martian Surface EVAs (MEVA)**	**Environmental**
	Occurrence RangeMin: First observed occurrence of condition **Occurrence RangeMax** Last observed occurrence of condition	occurrence of condition						probability given environmental exposure **Beta.alpha:** alpha parameter of beta distribution for condition probability given environmental exposure **Beta.beta:** alpha parameter of beta distribution for condition probability given environmental exposure
Data Source	SME, LSAH	SME, LSAH	SME, Analog data, LSAH, Terrestrial Models	SME, Analog data, LSAH, Terrestrial Models	LSAH, Terrestrial models	LSAH, Terrestrial models	LSAH, Terrestrial models	Inherited from IMM, PRA models, Terrestrial Models
Conditions	<u>SAS Conditions:</u> • Back Pain (ICL91) • Constipation (ICL92) • Epistaxis (ICL93) • Headache (ICL94) • Insomnia (ICL 95)	• ICL61 - Gravity Well – Neurovestibular Disturbance • ICL62 - Gravity Well – Orthostatic Intolerance • ICL122 - Gravity Well – Entry Motion Sickness	• ICL112 – Trauma - Abdominal Injury (Blunt) • ICL113 – Trauma – Chest Injury (Blunt) • ICL114 – Trauma – Minor Head • ICL115 - Trauma – Severe head • ICL116 – Traumatic	N/A	<u>EVA Related Conditions:</u> • DCS (ICL39) • Dehydration (ICL40) • Fingernail Delamination (ICL41) • Hand Injury (ICL42) • Heat Illness (ICL43) • Paresthesia (ICL44) • Shoulder Injury (ICL45)	<u>EVA Related Conditions:</u> • Decompression Sickness (ICL39) • Dehydration (ICL40) • Fingernail Delamination (ICL41) • Hand Injury (ICL42) • Heat Illness (ICL43) • Paresthesia (ICL44)	N/A	ICL36a – Dust exposure – Lunar (EVA crewmember) ICL 36b – Dust exposure – Lunar (non-EVA crewmember) <u>SPE</u> • ICL4 - Acute Radiation Syndrome <u>Smoke/Toxic Gas</u> • ICL110 - Toxic Inhalation Exposure • ICL111 – Toxic Inhalation Exposure

	Category 1				Category 2			Category 3
Grouping	**SAS**	**Gravity Well Transition**	**Lunar Surface Operations**	**Martian Surface Operations**	**Space EVAs (SEVA)**	**Lunar Surface EVAs (LEVA)**	**Martian Surface EVAs (MEVA)**	**Environmental**
	• Nasal Congestion (ICL96) • Space Motion Sickness (ICL97) • Urinary Retention (ICL98)		Hypovolemic Shock		• Suit Contact Injury (ICL46)	• Shoulder Injury (ICL45) • Suit Contact Injury (ICL46) <u>Fracture Conditions:</u> • Arm (ICL51) • Cervical Spine (ICL52) • Distal Leg (ICL53) • Femur (ICL54) • Hand (ICL55) • Wrist (ICL56) • Thoracic/ Lumbar Spine (ICL57)		– Combustion Products

3.3.3 Crew/Vehicle Characteristics and Condition-Specific Classifications

In addition to DRM-specific factors impacting condition-specific incidence as outlined above, incidence can be affected by certain medical disorders that may be diagnosed prior to or during spaceflight missions. For instance, only crewmembers who have required a dental crown(s) for a pre-flight medical condition can lose a dental crown(s) inflight. Further, some condition incidences are modified by sex; for example, female astronauts experience an increased incidence of urinary retention during spaceflight compared to their male counterparts. Similarly, some conditions are sex-specific (e.g., abnormal uterine bleeding is a uniquely female condition whereas acute prostatitis is uniquely male). The model accounts for these differences by allowing certain crew characteristics to alter baseline medical condition incidence.

IMPACT 1.0 designates crew characteristics (formerly referred to as "attributes" in iMED) as follows:

- Sex (male/female)
- Contacts (presence or absence of contact lenses)
- Dental crowns (presence or absence of dental crowns)
- Pregnancy (ability of a crew member to become pregnant)

In the process of EL development, the iMED crew characteristics for prior abdominal surgery and coronary artery calcium (CAC) score were removed. Abdominal surgery was removed because the incidence of ICL90 – Small Bowel Obstruction is based on terrestrial data that includes patients who have had abdominal surgery in the past and those who have not. The data to support a separate incidence based on prior abdominal surgery were not available. The CAC score is accounted for within IMPACT because it is included in the Astro-CHARM©[21] model that was used to generate the incidence for ICL3 – Acute Coronary Syndrome and ICL85 – Shock - Cardiogenic. New characteristics for the presence of a mixed sex crew as a mission input were added. As the team performs literature reviews for future IMPACT versions, it is possible that new characteristics may be identified, or existing characteristics will require refinement. In this event, a quorum of members from the ExMC EL team will meet to discuss for inclusion. If agreed, project stakeholders will be consulted, and this document updated to reflect approved changes.

3.4 ESTIMATES OF MISSION END-STATES

Three mission end-state results are addressed using data from the EL: removal to definitive care (RTDC),loss of crew life (LOCL), and task time lost (TTL). For this version of IMPACT, no consideration is given to the availability of a return vehicle or the likelihood of a successful clinical outcome for the RTDC end-state.

3.4.1 Removal to Definitive Care (RTDC)

The Return to Definitive Care (RTDC) end state in IMPACT refers to the point where; the capabilities necessary to treat the specified condition exceed those of the on board medical system; there is a high probability of a time sensitive, clinically significant adverse outcome; and definitive care has a reasonable chance of preventing the adverse outcome. For the purposes of finding data related to RTDC for the CLiFFs, RTDC surrogates were determined for each condition. Initially, many of the surrogates included the "need for hospitalization" or "need for surgery." Using these surrogates may lead to overestimation of RTDC probability because some care that would typically require hospitalization terrestrially (e.g., IV antibiotics or fluids) may be possible during spaceflight. In addition, operational decisions made during the mission may delay surgery if the procedure can be safely delayed until the end of mission. Conditions that may lead to RTDC could include any of the following criteria:

[21]Astro-CHARM. 10-Year ASCVD Risk Calculator with Coronary Artery Calcium. Astrocharm.org. 2022.

- Potential loss of crew life
- Potential significant permanent impairment
- Potential intractable pain

These indications are determined by SME knowledge of disease progression, operational considerations and data from the rapid systematic review approach outlined in Section 3.2 using the best-case/worst-case scenario definitions. RTDC is reported as a percent probability with maximum/minimum bounds.

While the determination of a RTDC event is difficult to ascertain for all conditions prior to occurrence during spaceflight, surrogate terrestrial situations may be used to determine the likelihood of RTDC. The ICL 1.0 conditions were reviewed by SMEs from the EL Team prior to the rapid systematic review. Some conditions were judged to require RTDC with 100% probability by the SMEs. These were annotated and for these conditions RTDC literature searches were not performed. For the remaining conditions, EL SME knowledge was utilized to determine appropriate RTDC surrogates (e.g., requirement for hospitalization or surgical intervention). This surrogate was used during the rapid systematic review and ultimately RTDC probability was based on the resulting literature.

3.4.1.1 Loss of Crew Life (LOCL)

The loss of crew life (LOCL) end-state is reached when the affected crewmember dies due to a medical condition. This is reported as a percent probability with maximum/minimum bounds (uniform distribution). Supporting evidence was collected via the rapid systematic review approach outlined in Section 3.2 and supplemented where necessary with SME input.

3.4.1.2 Task Time Lost (TTL)

Task time lost (TTL) is a metric calculated by MEDPRAT to estimate the amount of crew work time lost due to a medical event. It is based on Clinical Phase (CP) Duration and Task Impairment (TI) (Sections 3.6 and 3.6, respectively). TTL is calculated by multiplying the TI value by the Clinical Phase 2 (CP2) clinical phase duration (time). During reviews of TTL it was noted that TI does not remain constant during CP2 (treatment phase). As described in more detail in section 3.6.1.5, TI decreases with treatment, and a modification was made to the value of TI to represent this observation:

$$TTL = (TIinitial + TIfinal) \times CP2time/2$$

(*TIinitial* represents the task impairment at the beginning of CP2 and *TIfinal* represents the task impairment at the end of CP2; CP2time is the duration of the CP2, or treatment phase). TTL replaces “Quality Time Lost” (QTL), a metric calculated by IMM. More details about calculating Task Time Lost can be found in the MEDPRAT Software Design Document referenced in Appendix A Reference Documentation

3.5 CLINICAL PHASE DURATIONS

Clinical phases describe how long the effects of a condition last within the simulated mission. They inform both the TTL endpoint and the consumption of resources (Section Clinical Capabilities, Resources, Resource Equivalence, and Resource to Capability Matrices). Each condition progresses through three clinical phases, and each phase is expressed in units of hours. This architecture was derived from the legacy IMM clinical phase structure and has not been substantially altered. However, the method used to derive each duration has been made more transparent and evidence- based.

Clinical Phase 1 (CP1) is the period of time required for the initial assessment and diagnosis of the affected crewmember. During this phase, the crewmember is not able to perform any assigned spaceflight tasks and is thus assigned 100% TI. This duration is derived by SME estimation of the time needed for a clinician to perform an assessment and diagnosis for the specific condition. CP1 durations were assigned by the CRT working group of the EL Team (Section 4.5.5.2). CP1 durations were recorded as discrete values.

Clinical Phase 2 (CP2) is the period of time required for treatment and convalescence. This phase also encompasses relapses or reoccurrences necessitating additional treatment. CP2 applies to both the acute and chronic stages of the condition and is reflected as a range of time (i.e., a minimum and maximum duration). These values were derived from medical literature using the rapid systematic review approach outlined in Section 3.2. All conditions progress to Clinical Phase 3.

Clinical Phase 3 (CP3) is defined as the end-state and is reached once the affected crewmember has either fully recovered, recovered to the maximal extent with persistent Task Impairment (TI), died (LOCL), or triggered consideration of an evacuation (RTDC). CP3 is calculated by MEDPRAT as a discrete duration of time lasting from the end of CP2 until the end of the mission.

3.6 TASK IMPAIRMENT

3.6.1 IMM Functional Impairment Limitations

The IMM captured the degree to which a crewmember affected with a medical condition is impaired through a value called Functional Impairment (FI). FI is recorded as a percentage and reflects the severity of the medical condition in terms of the ability of the crewmember to perform daily activities. FI was estimated by applying criteria from the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment, Sixth Edition, to each medical condition on the IMM condition list.[22]

The IMM approach has several notable limitations:

- The AMA Guides are designed for use in medical conditions with static, permanent impairment,which is assessed at the point of maximum medical improvement. Most medical conditions occurring in spaceflight inflict temporary, not permanent, impairment.

- The AMA Guides were created using terrestrial activities of daily living (ADLs). Although spaceflight encompasses ADLs, complex tasks related to spaceflight and exploration are not accounted for by the AMA Guides.

- The IMM method required SME interpretation to modify the AMA Guides to be suitable for spaceflight. This was particularly true with regards to dental conditions and conditions involvingpain. Dental conditions utilized a modified version of the AMA Guides: The American Association of Oral and Maxillofacial Surgeons (AAOMS) Guidelines to the Evaluation of Impairment of the Oral and Maxillofacial Region.[23] Medical conditions involving pain utilized the Complex Regional Pain scoring method contained within the AMA Guides. This method assigns impairment for pain in either the upper or lower extremities. All conditions involving pain, regardless of whether it was in an extremity, utilized this scoring. Conditions involving a body region above the waistline utilized the upper extremity scores and regions below the waistline utilized the lower extremity scores.

3.6.1.1 Task Impairment: A New Paradigm

Given the limitations of the FI methodology used for IMM, a new paradigm has been created for IMPACT, Task Impairment (TI). Advantages of this method include its focus on spaceflight specific tasks rather than terrestrial ADLs, the potential to drive a loss of mission metric in the future, the fidelity to assess TI subdivided by mission phase in future iterations of IMPACT, and the ability to readily update TI values as anticipated mission tasks change. Further, after initial SME input, this method has the potential to be software driven. For IMPACT 1.0, TI provides a discrete percentage value that considers a decrease in TI as a crewmember undergoes treatment for a specific medical condition.

[22]Rondinelli, R. (2014). *Guides to the evaluation of permanent impairment*. Chicago, IL: American Medical Association

[23]Guidelines to the Evaluation of Impairment of the Oral and Maxillofacial Region. (2018). Retrieved November 01, 2020, from https://www.aaoms.org/docs/practice_resources/clinical_resources/impairment_guidelines.pdf

3.6.1.2 Clinical Phases

IMPACT 1.0 assumes three clinical phases. Clinical Phase 1 (CP1) is the diagnostic phase in which the severity of a medical condition has not yet been established. During CP1 a crewmember would not be performing tasks of any kind and thus is assigned 100% TI. Clinical Phase 2 (CP2) is the active treatment, recovery, and convalescent phase for a given medical condition. This phase includes pharmacologic and procedural treatment modalities, along with the ensuing recovery period. Clinical Phase 3 (CP3) is defined as the maximal resolution phase. In CP3, the crewmember has recovered to the best of his/her ability, and any resulting impairment is permanent (or cannot be further improved during the mission).

3.6.1.3 Task Impairment (TI) Methodology

The process of determining TI for each of the 119 conditions on the ICL 1.0 can be subdivided into 5 discrete steps. These steps are illustrated in Figure 3. An explanation of each step follows.

STEP 1: IDENTIFYING HUMAN SYSTEM TASK CATEGORIES ON THE MARS TASK LIST

The basis of the TI method is The Human Exploration of Mars: Preliminary List of Crew Tasks document. For the purposes of this methods document, this will herein be referred to as the "Mars Task List" (MTL). This document was created by NASA's Human Research Program, Human Factors and Behavioral Performance Element, and has been utilized by the agency as a source of anticipated crew tasks for a mission to Mars. The list contains approximately 1,200 tasks separated into 12 mission phases. To prevent artificially inflating TI, tasks that were identical across multiple mission phases were removed. This occurred in outbound and return to Earth phases of flight in which most of the tasks were identical. Unique tasks were retained. The MTL was then reviewed by EL Team SMEs and 18 unique Human System Task Categories (HSTC) were developed. HSTCs either mirror human terrestrial capabilities (i.e., cognitive – simple, cognitive – complex, interpersonal skills, communications, vision, hearing, cardiopulmonary, dentition, gastrointestinal, genitourinary, hand – dominant, hand – any, upper extremity, lower extremity, and ambulation and standing in gravity) or include spaceflight-specific categories (i.e., translation and stabilization in microgravity, don/doff equipment, pressure ops). TABLE 8 presents the HSTCs and associated definitions as created by the SMEs.

STEP 2: MARS TASK LIST (MTL) TASKS ASSIGNED TO HUMAN SYSTEM TASK CATEGORIES

After identification of the HSTCs, each task on the MTL was assigned to the relevant HSTCs needed to complete the task by EL Team SMEs. This assignment does not signify 100% impairment of the task if the affected HSTC is involved in a medical condition, but rather that the task could not be performed nominally.

STEP 3: TALLY TOTAL HUMAN SYSTEM TASK CATEGORIES

After applying the above process, the total number of tasks assigned to each HSTC were determined ("HSTC Total"). These HSTC Totals were then combined to determine the "Total Mission Tasks" (TMT) across all HSTCs (Figure 3). There are 3763 TMT. TMT served as the denominator for the TI calculation in Step 5. Note that the TMT is larger than the number of tasks on the MTL (approximately 1200 tasks) because each task can map to more than one HSTC.

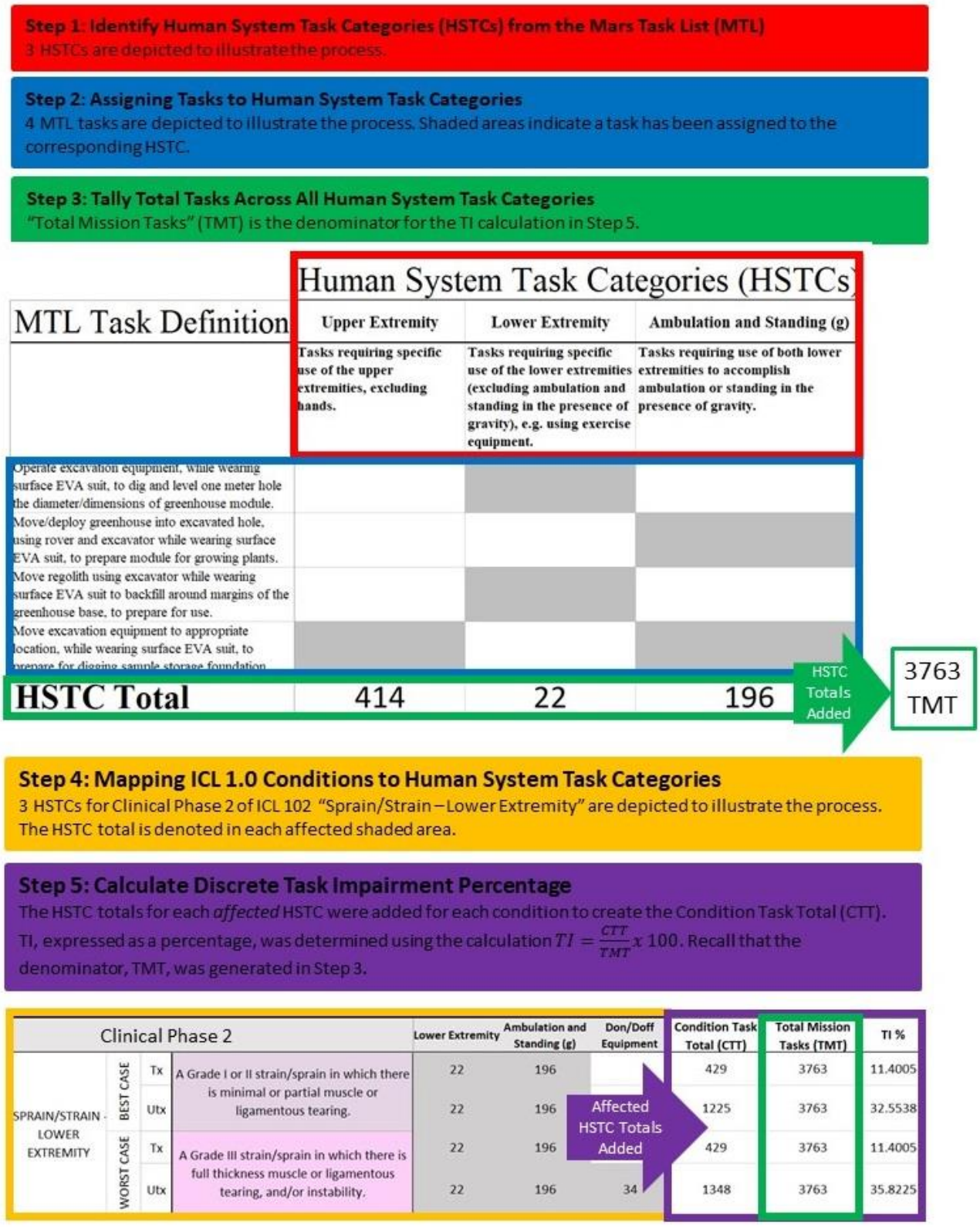


Figure 3 Overview of Task Impairment Process

TABLE 8 HUMAN SYSTEM TASK CATEGORIES (HSTCs) AND DEFINITIONS

Based on the Human Exploration of Mars: Preliminary List of Crew Tasks.

Human System Task Category	Human System Task Category Definition
Cognitive - Simple	Tasks requiring simple cognitive involvement (low levels of attention, following simple checklists, and not requiring extensive decision making) in conjunction with inputs from other systems.
Cognitive - Complex	Tasks requiring complex cognitive involvement (requiring constant attention, frequent interpretation of outside stimuli to inform real-time situations) in conjunction with inputs from other systems.
Interpersonal Skills	Tasks requiring personal, social interaction between crew, including complex technical tasks that require crew interaction.
Communications	Tasks requiring primarily communication, via hearing and speaking.
Vision	Tasks in which visual information is required.
Hearing	Tasks in which primarily auditory information is required, excluding communication (e.g., hearing alarms, medical auscultation, on orbit hearing assessments).
Cardiopulmonary	Tasks requiring greater-than-baseline cardiopulmonary effort, (e.g., physically strenuous activities).
Dentition	Tasks requiring use of teeth for mastication.
Gastrointestinal	Tasks requiring use of the alimentary system (e.g., solids/liquids consumption and solids excretion).
Genitourinary	Tasks requiring use of the male/female genitourinary systems.
Hand (dominant)	Tasks performed using primarily the hand, requiring use of the dominant hand.
Hand (any)	Tasks performed using primarily the hand(s), with no preference for dominance, with equivalent bilateral effectiveness.
Upper Extremity	Tasks requiring specific use of the upper extremities, excluding hands.
Lower Extremity	Tasks requiring specific use of the lower extremities (excluding ambulation in the presence of gravity).
Ambulation and Standing (g)	Tasks requiring use of both lower extremities to accomplish ambulation or standing in the presence of gravity.
Translation and Stabilization (microgravity)	Tasks requiring use of either the upper or lower extremities to accomplish translational movement and stabilization (securing oneself to remain stationary) in the setting of microgravity.
Don/Doff Equipment	Tasks requiring the donning/doffing of personal equipment (including pressure suit, exercise harness, EVA equipment, etc.).
Pressure Ops	EVA/contingency tasks performed while pressurized in a suit.

STEP 4: MAPPING ICL 1.0 CONDITIONS TO HUMAN SYSTEM TASK CATEGORIES

With Steps 1-3 completed, the 120 medical conditions on the ICL 1.0 were mapped to the relevant HSTCs. This was performed by EL SMEs for Clinical Phase 2 and 3, for both best and worst-case, treated and untreated scenarios. These assignments were made during working meetings lasting up to two hours in duration, occurring 1-2 times per week over a 3-month period. Six specific criteria were used as guidelines (TABLE 9). If the answer to any criteria 2-6 was "yes," then the HSTC was affected.

TABLE 9 CRITERIA FOR ASSIGNMENT OF CONDITIONS TO HUMAN SYSTEM TASK CATEGORIES

1. *When the best-case scenario or worst-case scenario includes a spectrum of the condition, the most common presentation for the scenario should be used.*
2. *Is the affected crew member physically incapable of performing the HSTC, without impairment, with the condition?*
3. *Would the treatment (e.g., medications) impair the crewmember's ability to perform the HSTC? (Does not apply to untreated conditions)*
4. *Does the condition have a high likelihood of causing a significant aeromedical contraindication with an associated HSTC?*
5. *Would performing tasks in an associated HSTC worsen the condition?*
6. *Does pain associated with the condition impair any further HSTCs?*

STEP 5: CALCULATE DISCRETE TASK IMPAIRMENT PERCENTAGE

After SME consensus on all components of Step 4 was achieved, the number of tasks impaired by a given condition (the sum of all affected HSTC Totals for that condition), known as the "Condition Task Total" (CTT) was determined for the four variants of each condition (best and worst-case, treated, and untreated scenarios). For example, in ICL8 – Appendicitis, during Clinical Phase 2, for the best-case treated scenario the resulting CTT is 1622 tasks. The CTT is then used as the numerator, with the TMT from Step 3 (3763) as the denominator, to calculate a definitive TI. This calculation becomes 1622/3763, resulting in a TI of 43.1% in CP2 for a best-case treated appendicitis. This was repeated for all variants of each of the 120 ICL 1.0 medical conditions, for CP2 and CP3. (Recall CP1 assumes 100% TI for all conditions).

3.6.1.4 TI Nomenclature

To transparently convey that the methodology behind TI is unique from FI, ExMC recommends new nomenclature as follows:

- "Task Impairment" (TI) to replace "Functional Impairment."
- "Task Time Lost" (TTL) to replace "Quality Time Lost."
- "Crew Task Index" (CTI) to replace "Crew Health Index"

Although the nomenclature for Task Time Lost and Crew Task Index (CTI) is recommended to be changed, these values would be calculated using the same formulas that were used with IMM. Note that CTI has the potential to drive a future loss of mission metric. The EL Team strongly recommends against comparison of the new CTI to the old Crew Health Index, primarily because of the changes to the medical conditions in ICL 1.0 as compared to the

IMM condition list. Additionally, the method of using tasks for impairment instead of AMA ADLs will limit comparability.

3.6.1.5 TI Limitations and Future Work

There are limitations to the new TI approach. It is important to note that TI does not refer to the proportion of tasks that a crewmember would be unable to perform under any circumstances. Rather, TI refers to tasks which could not be performed without some level of impairment. This was discussed at length when planning the architecture of TI. It is not feasible for SMEs to assign a degree of impairment during step 4 of the process. Thus, it was determined that TI would represent off-nominal tasks, indicating some degree of impairment but not providing a specific degree of impairment within each HSTC or within individual tasks.

TI is driven by the MTL. The MTL is a preliminary document of SME-derived tasks necessary for a Martian mission.[24] IMPACT 1.0 has been designed for a 210-day cis-lunar Artemis mission with 30-60 days on the surface of the Moon. After completing the TI project, concern was raised regarding the applicability of the MTL to the defined lunar DRM. Thus, the process was reviewed and tasks that were specific to a Martian Mission were removed to better approximate the defined lunar DRM. Missions in the defined DRM do not plan to include a lunar habitat separate from the launch/landing vehicle. Thus, tasks specific to a Martian habitat were removed. Due to similar constraints for the defined DRM, tasks specific to operating heavy machinery (e.g., excavators, drilling equipment, etc.), growing food, operating a robot, and using a 3D printer were omitted. Tasks that were specific to Mars, such as analyzing soil samples for biologic signs of life, were also removed. Finally, medical tasks that were outside the defined scope of resources and treatments for IMPACT 1.0 were removed (e.g., performing surgery). TI was then re-calculated with the remaining conditions on the MTL to better approximate the IMPACT 1.0 DRM. This exercise had little effect on TI. In Clinical Phase 2 and Clinical Phase 3, 98.2% and 99.6%, respectively, of TI values were unchanged or had an absolute change of less than 3%. Thus, it was determined that the current set of MTL tasks that was described in this manuscript would be retained for TI for IMPACT 1.0 and future iterations of IMPACT will plan to use DRM specific tasks where possible. When tasks for Artemis missions are known, they should be used instead of the MTL.

In future iterations of IMPACT, Crew Task Index (CTI), formerly “Crew Health Index” with IMM, may be skewed depending on the DRM assigned for IMPACT missions unless mindful calculation of TI is made based on mission phases (e.g., if the DRM does not include surface operations, then the TI would be inaccurate if the surface operation phase of the MTL is included in the TI calculation). Using mission phases to customize TI is recommended in the future. This can be easily accomplished as the MTL is currently divided into 12 mission phases that will expedite customizing TI by mission phase in the future.

TI is versatile in that it can be recalculated based on the tasks identified for inclusion. This provides the opportunity for increased fidelity for separate mission phases in future iterations of IMPACT 1.0. Recalculating TI is straightforward and can be accomplished in less than a day if tasks are removed. However, if entirely novel tasks (not part of the MTL) are added to a planned mission, steps 2-5 of the process outlined in the methods section will need to be undertaken to recalculate TI for all conditions. If an added task falls under an already existing task on the MTL, this process will not need to be repeated. Similarly, if new conditions are added to the ICL, steps 4-5 must be repeated.

Due to project time constraints, TI was designated prior to the CP2 duration assignments. Upon review, for many conditions, the duration of CP2 alters SME perception regarding involved HSTCs, in turn, altering TI. As a result of this review, a reworked calculation of task time lost (see equation and explanations below) was implemented that was felt to be more operationally faithful.

Task Time Lost (TTL) is a metric within the IMPACT system intended to estimate mission relevant disability. For a single condition it is calculated via the following equation:

[24] J. Stuster, J. Adolf, V. Byrne, M. Greene, Human Exploration of Mars: Preliminary Lists of Crew Tasks, National Aeronautics and Space Administration, Johnson Space Center, 2018 ntrs.nasa.gov/citations/20190 0 01401 (accessed May 11, 2022)

$$TTL = (CP_n\ TI\%) \times (CP_n\ Duration)$$

Where CPn TI% is the percentage of mission tasks potentially affected by the condition in the designated clinical phase (CP) and CPn duration is the length of time associated with the designated clinical phase.

Since medical treatment affects both TI% and CP duration for nearly every condition, this is one of the most sensitive metrics in the IMPACT model and has a significant effect on resource optimization and mission risk reporting. During the clinical validation of the IMPACT tool, (using Medical Database Lockdown (LD) 128) two inaccuracies were identified that potentially affect the TTL metric. These were corrected in LD149, as described below. A LD is a static copy of the IMPACT Medical Database at a specific point in time that is used to perform IMPACT simulations.

The first identified issue was that by using static percentages for each clinical phase the modelled "patient" recovers instantaneously once the CP2 duration has elapsed within IMPACT. Few medical conditions behave like this in the real world, as recovery is often gradual. Modeling recovery as instantaneous in IMPACT is likely to substantially inflate the impairment for conditions in the model and lead to unrealistically high TTLs. Prior to this modification for LD 149, a patient would have their maximum impairment throughout the entirety of CP2 and then suddenly recover as opposed to a gradual reduction in impairment over the course of CP2. In order to address the first inaccuracy, the Exploration Medical Capability Clinical and Science Team (CST) clinicians determined that replacing the original CP2 TI% value with the mean value for the CP2 TI% and CP3 TI% would be an effective way to model a gradual recovery. This calculation functionally models a linear recovery with CP2 TI% as the maximum and CP3 TI% as the minimum.

In lockdown 128, for example, a condition with 50% impairment at the beginning of CP2 with CP2 lasting 10 days would instantaneously drop from 50% to 0% impairment once 10 simulated mission days have elapsed. In a more realistic scenario, at the initiation of treatment, a patient may have 50% impairment on day 1, then recover to 25% impairment on day 5, 13% impairment on day 7, and so on until fully reaching the point of maximum recovery at the end of CP2 for the given condition. A change was made in this calculation to improve the fidelity of the TTL estimate and was incorporated into LD 149. For simplicity, a linear improvement in TI% is presumed as treatment progresses during CP2. The maximum TI% exists at the start of CP2 and decreases linearly to the recovery (CP3) value at the CP2-CP3 transition point. Mathematically, the decrease in TTL is described by: (TI% at the start of CP2 – TI% at the end of CP2)/2. Thus, the maximum change possible that could occur for any condition is a 50% decrease in TTL. This only happens if the TI% at the end of CP2 is 0%. The difference seen in TTL between LD 128 and 149 was a decrease of 39.1%. The magnitude of these changes was consistent with our expectations.

The second identified inaccuracy stems from the fact that IMPACT treats the CP2 duration in its database as a "maximum" duration and will not exceed the mission days remaining. For example, if a condition occurs with only 10 days left in the mission, but the CP2 duration for that condition is 210 days, IMPACT will calculate TTL using only the 10 mission days remaining. During the assignment of clinical phase duration some clinicians misunderstood this calculation and artificially capped their assigned conditions with long CP2 durations at 210 days which is the IMPACT 1.0 notional DRM duration. IMPACT may underrepresent TTL for these conditions if there are more than 210 days in the simulated mission.

To address this second inaccuracy, the same clinician team reviewed the list of IMPACT conditions with CP2 maximum durations lasting exactly 210 days. If the 210-day value was determined to be based on evidence from the original literature search, it was left as is. If this value was found to be an artificial cap, the original literature search data was identified and the CP2 duration values replaced with the evidence-based values.

The result of these changes should refine the accuracy of the TTL calculation.

Limitations inherent to calculation of TTL include no consideration of Crew Medical Officer (CMO) time lost and also that TTL does not consider how the crew would reassign tasks. For example, if a crewmember had TI for one task, he could increase the time he/she spends on other tasks, thus freeing time for other crewmembers to perform

the task that can't be done by the injured crewmember. This could reduce total crew incapacity by a significant amount.

The designation of TI as a discrete number, instead of a range, results in an underestimation of the uncertainty in the determination of TI. Because of time constraints, TI was calculated by dividing the number of affected tasks caused by occurrence of the condition by the total number in the task list. There exists uncertainty in the number of tasks that are actually affected by a condition as there are gradations in the severity of each condition within the "Best Case" and "Worst Case" categories. Ideally, a range should be used for future calculations for TI; this would better capture the uncertainty of this input. Finally, in the equation above for TTL, TI is multiplied by each clinical phase duration. The minimum and maximum values for CP2, for example, can vary considerably. This introduces a large amount of uncertainty into the calculation of TTL.

3.6.1.6 TI Operational, Internal Vetting

With assistance from ExMC leadership, the EL Team developed a process for internal vetting of the TI values. The goal was to have an operational flight surgeon perform the following task. To minimize the time necessary for this task, four conditions were chosen (ICL3 – Acute Coronary Syndrome, ICL17 – BHP - Psychosis Secondary to Depression, ICL28 – Dental Abscess, and ICL39 – EVA Related Decompression Sickness) that represent medical, dental, behavioral health and performance, and EVA specific conditions. For two of the conditions, the best-case scenario was selected (ICL3 and ICL17). Further, for two conditions the treated scenario was selected (ICL3 and ICL28). Thus, the following conditions and associated scenarios were selected:

- ICL3 – Acute Coronary Syndrome, Best-Case Treated Scenario
- ICL17 – BHP – Psychosis Secondary to Depression, Best-Case Untreated Scenario
- ICL28 – Dental Abscess, Worst-Case Treated Scenario
- ICL39 – EVA Related Decompression Sickness, Worst-Case Untreated Scenario

The operational flight surgeon was provided with a representative sample of 10% of the tasks on the MTL and asked to indicate (yes or no) whether the task could be performed with the given condition and associated scenario. The criteria that the flight surgeon was instructed to use to guide this process were the same as the criteria used by the TI working group, detailed in TABLE 9. After completion, ExMC planned to compare the results from this process to the results obtained by the TI working group to see how they compare. If concurrence of 75% was not reached, then this would suggest a revision in Step 2 of the TI process outlined above. This task was assigned to an operational colleague matrixed to ExMC. Unfortunately, the operational tempo at NASA JSC is currently such that this task was never completed. Thus, it has become forward work.

4.0 CONDITION OCCURRENCE, SCENARIOS, CAPABILITIES/RESOURCES AND THE QUALITY/MAINTENANCE OF THE EVIDENCE

4.1 OVERVIEW

MEDPRAT simulates condition occurrence throughout mission time, the condition's progression to a best or worst-case scenario, the mitigating effects of treatment versus no treatment, the end-states of recovery, RTDC or LOCL, treatment and recovery duration, and the TI of the affected crewmember by clinical phase of the condition. The EL team drew on IMM legacy data with collection of updated data to inform probability distributions to improve model predictions. Data was collected to inform the stochastic features described in the following sections.

4.2 CONDITION OCCURRENCE

Data on condition incidence and measures of variability appropriate to the specific conditions were collected from the scientific literature. They were used to inform which model distributions are utilized to generate occurrences

(e.g., Binomial or Poisson) in conjunction with biostatistician support and input from the modeling team. The choice of distribution for occurrences (Poisson or Binomial) is determined by the MEDPRAT modeling team in conjunction with the EL team and based on the type of conditions being modeled as described in Section IMPACT Condition Groupings. IMPACT Condition GroupingsFurther, incidence rate and proportion distributions were defined for each specific condition.

The available parameters also inform which distributions are utilized to generate estimates in the MEDPRAT Monte Carlo simulations within IMPACT. While the specific type of data collected vary based on what is available in the published literature, relevant data to inform model probabilities (incidence) include the following:

- Total number of observed events and person-years or person-tasks
- Incidence rate or proportion estimates and uncertainty estimates (i.e., standard errors orconfidence limits)
- Point or period prevalence estimates and uncertainty (i.e., standard errors or confidence limits)
- Model-based predictions of incidence rates or proportions

The data above are used to define the distributions that inform condition occurrences and medical outcomes for individual mission simulations. Reported outcomes are a summary of thousands of individual "missions" based on Monte Carlo simulations.

4.3 BEST-CASE, WORST-CASE SCENARIOS

As a Monte Carlo simulation, MEDPRAT utilizes specified probability distributions to determine how often a medical condition occurs and what proportion of those occurrences progress to a best or worst-case scenario. The probability is informed by evidence-based data. When evidence was available to support a discrete proportion, it was used. For many conditions, a discrete proportion was not supported by the literature. In these cases, a range was specified in accordance with the evidence. In the absence of any literature to inform the probability, SME input was used. The model uses a uniform distribution with upper and lower percentage bounds to account for the uncertainty in relying upon SME input or in the supporting literature. When a condition occurs, the model uses a Bernoulli distribution applied to the worst-case percentage parameter to determine whether the condition goes down the best or worst-case pathway for a given simulation. The EL team assigned best and worst-case probability for all ICL 1.0 conditions.

4.4 TASK IMPAIRMENT AND DURATION

The degree of Task Impairment (Section 3.6) and the Clinical Phase duration are used to calculate Task Time Lost (TTL) (Section 3.4.1.2). TTL is calculated for each clinical phase (Section 3.5) by multiplying the TI and duration for the phase. The mission TTL is the sum of these values for each condition across all three clinical phases.

4.5 CLINICAL CAPABILITIES, RESOURCES, RESOURCE EQUIVALENCE, AND RESOURCE TO CAPABILITY MATRICES

4.5.1 Overview

The Capability Resource Table (CRT) is designed to facilitate the translation of medical treatment into engineering FoM such as mass and volume. It contains a list of all cognitive and procedural capabilities necessary to diagnose, stabilize, and manage the specified medical condition and the resources associated with each capability. When available, CRTs were based on published, evidence-based practice guidelines and adapted by EL SMEs to the specific condition's definition and the limitations of the spaceflight environment. When practice guidelines were not available, a minimum of three SMEs with clinical experience related to the condition (e.g., ophthalmology and aerospace medicine for SANS) reached consensus to create the CRT.

Each listed capability represents a skillset or action and is associated with the resources necessary to perform that action. In some cases, resources are linked to alternatives that may be substituted should the primary resource be unavailable due to the optimization algorithm or being depleted during the simulation. The CRT also contains the parameters necessary to instruct MEDPRAT how to use each capability and resource including: necessity, contribution, efficacy, equivalence, primacy, quantity, dose frequency, and the training level required to perform the capability.

4.5.2 Capabilities

Capabilities are discrete skillsets, tasks, and/or actions (e.g., “interpret laboratory data” or “deliver intravenous antibiotics”) associated in the model with standardized collections of resources. They serve as a method for summarizing practice guidelines, ensuring no aspect of care is overlooked, streamlining review, and standardizing resources across conditions. Taken together, they provide a list of all required skills and actions a provider needs to manage the associated condition and inform the medical system requirements for the design reference mission. MEDPRAT treats capabilities as non-alternate treatment clusters as defined in the following section.

CAPABILITY MODEL PARAMETERS

Parameters associated with capabilities include: Capability Class, Capability Category, Scope of Practice Code (SoP), Contribution, Necessity, Equivalence, Primacy, and Efficacy. These parameters govern how capabilities are treated by the model and are explained in TABLE 10.

4.5.3 Resources

Resources are defined as a specific skill, item, substance, and/or knowledge base (e.g., 20-gauge intravenous catheter, pseudoephedrine 60mg, or “interpretation – physical exam”). These allow engineers to assign the FoMs MEDPRAT uses to perform the trade space analyses. Resources were organized as either individual items or grouped together as non-alternate or alternate treatment clusters.

NON-ALTERNATE TREATMENT CLUSTERS (BUNDLES)

A non-alternate cluster requires all listed resources for the cluster to be available for the capability and the condition to be “treated” (e.g., an intravenous antibiotic stored in a powder form cannot be administered without the diluent used to reconstitute it). In this case if the mass and volume limitations imposed by the MEDPRAT simulation have eliminated a required resource, or it has been depleted during the simulation, the capability cannot be performed, and the condition will remain untreated.

ALTERNATE TREATMENT CLUSTERS (EQUIVALENT RESOURCES)

Alternate treatment clusters enable some capabilities to be accomplished in multiple ways using collections of different resources. For example, a simple skin laceration may be closed with skin adhesive, adhesive bandages, or sutures. Similarly, a wrist splint can be fabricated from either plaster, fiberglass, or a rigid object with tape. This structure allows substitutions within the MEDPRAT engine, enabling the model to preserve essential capabilities even when the default or “ideal” resource is not available. This also gives MEDPRAT some ability to model improvised solutions when equipment is not available, provided SMEs have assigned the necessary resources within the CRT, (e.g., using a belt as a tourniquet).

Improvised care solutions are a widespread practice of providers in resource-limited environments, and it is reasonable to expect that creative use of existing equipment will be part of a deep space mission. Accounting for such creativity within alternate treatment clusters increases the fidelity of the model, may reduce the mass and volume requirements of the medical system, and may help generate an SME informed list of contingency solutions if supplies are exhausted on a mission. However, when using alternates, it is known that equivalence or efficacy may differ. These factors were taken into consideration as discussed below.

RESOURCE MODEL PARAMETERS

Parameters associated with resources include Contribution, Necessity, Equivalence, Primacy, Efficacy, Quantity, Duration, and Dose Frequency. These parameters govern how resources are treated by the model and are defined in the following section.

4.5.4 Model Parameters

The CRT model parameters instruct MEDPRAT how to use each capability and resource during the simulation. They inform MEDPRAT if a capability or resource bundle is an alternate cluster or a non-alternate cluster, the amount of resource required, and the effect the item has on outcomes. TABLE 10 provides an overview of the CRT model parameters.

TABLE 10 CAPABILITY RESOURCE TABLE MODEL PARAMETERS

Model Parameter	Description	Example
Capability Class	A placeholder parameter for capabilities developed in anticipation of future MEDPRAT functionality. It was not included in a functional form for IMPACT 1.0 and the assigned values are meant only as a functionality test for this effort. When formally assigned, the capability class is intended to enable a clinically relevant model of "partial treatment." This means a capability may affect all or only some of the MEDPRAT outcome metrics (LOCL, RTDC, and TI). While interim classes are assigned for each capability, these are notional and intended only for testing future functionality. Further work is needed to assign the fully functional classes.	A "Life Saving" capability could affect all outcome metrics while "Comfort" capabilities might affect only Task Impairment, and "Preventive" might alter incidence but have no direct effect on outcome metrics.
Capability Category	Defines capabilities as either "pharmaceutical" or "clinical." This was used to facilitate the review process outlined in Section Peer Review of Capabilities and Resources and is not a MEDPRAT parameter. It has no planned use or benefit beyond identifying capabilities that contain resources identified by SMEs as medications.	N/A
Scope of Practice Code (SoP)	Associated with all Capabilities, the SoP code represents the training level necessary to fulfill the capability. To facilitate validation, these represent 5 distinct terrestrial medical training curricula as listed in the example. This is planned to be implemented in future versions of IMPACT and is included in IMPACT 1.0 for testing.	1 = National Registry Emergency Medical Technician (EMT) – Basic 2 = National Registry Paramedic 3 = Certified Emergency Nurse or Critical Care Nurse 4 = Recent medical school graduate at the start of the first year of residency 5 = Generalist attending physician with acute care training and basic procedure skills (e.g., fully trained Emergency Medicine, Family Medicine, or Anesthesiology attending physician).
Contribution	The relative importance of each capability to the condition or each resource to its capability. When used, this allows for partial treatment risk reductions if some of the capabilities or resources are missing. For the IMPACT 1.0 effort, this was assigned a value of 1 to resources in all cases. The capability contribution value for IMPACT 1.0 is the sum of the number of resources required to treat the capability. This is due to the complications of assigning partial treatment values. An effort is currently underway to assign linearly ranked	In a condition with 4 resources assigned to a capability, each resource is assigned a contribution of 1 and the capability is assigned a capability of 4.

Model Parameter	Description	Example
	weightings to each capability in each condition by CST SME clinicians. The results of this effort will be reflected in IMPACT 1.1.	
Necessity	A measure of how necessary the capability or resource is to treat the condition. A necessity of zero means the condition can be fully treated even if the capability or resource is missing from the simulation, while 100% means the capability or resource must be present to treat the condition.	For IMPACT 1.0 the CRT working group treated this as a binary parameter (either 0% or 100%) due to the complications of assigning partial treatment values.
Equivalence	The amount of each resource required to perform the same function. Note, in most cases the CRT working group used the "quantity" and "dose frequency" parameters to capture this rather than equivalence.	Morphine 5 mg IV is equivalent to Hydromorphone 0.75 mg IV
Primacy	Relates to alternate clusters and represents the ranking order in which the resources should be used by the model. It is assigned an integer for alternate clusters and a "0" for non-alternate cluster items. This instructs the model which alternate resource should be allocated first based on SME input if multiple options exist for a given condition. If primacy is set to the same number for objects in an alternate cluster, the model will choose a resource at random.	If a wrist splint can be manufactured from fiberglass, plaster, or a rigid object and tape and all 3 exist in the simulation they may be assigned primacies of 1, 2, and 3 respectively. If fiberglass has been depleted in the simulation, MEDPRAT will use plaster instead. If neither is present it will assign the rigid object and tape. The condition will be untreated only if all three alternates are not available.
Efficacy	The percentage to which a resource provides a benefit. It permits an inferior resource to provide a partial benefit within the MEDPRAT model. Since evidence of this type is limited, particularly for spaceflight, the CRT working group only assigned a value less than 100% when there were robust studies identifying efficacy. This is an area where future teams may wish to focus to improve model fidelity since a dedicated effort may be able to identify more evidence. This would be particularly impactful for alternate clusters since lower efficacy will provide a consequence for "choosing" a particular resource beyond the primacy metric described above.	A medication may be 95% effective in treatment studies while its alternate may only be 70% effective.
Quantity	Represents the amount of a resource to be used per simulated occurrence. This parameter is best understood as the quantity needed and represents the amount of each named resource used based on dose frequency. For	The resource pharmaceutical Ibuprofen is listed as "Pharmaceutical – Oral – Ibuprofen – 200mg." The "quantity" in this case refers to the number of oral pills needed based on the recommended dosing schedule and the clinically desired amount of medication. If the intention in the CRT is to

Model Parameter	Description	Example
	pharmaceuticals, these resources were named with the smallest clinically relevant quantity included.	deliver 600mg of ibuprofen every 8 hours each day until the condition improves this resource would be listed as a quantity of 9 representing 3, 200mg pills, 3 times a day. This will be allocated for the duration of CP2.
Dose Frequency	Instructs MEDPRAT how to multiply the dose frequency. It is coded as: “event” in which the quantity is multiplied by one and represents a fixed amount to be given whenever the condition occurs; “per day” in which the SME clinician-assigned duration of the clinical phase is multiplied by the resource dosage required per day; or “end of mission” in which the per day quantity is multiplied by the remaining mission days.	Per event: Hydrocodone/APAP 5mg/325mg PO - 10 tablets per event for an injury. This will allot 10 total tablets for the condition. Per Day: See example of "per day" dosing above. This is allocated for the duration of CP2. End of Mission: This is the same as "per day," but instead of being allocated only for the duration of CP2, it is allocated for the remaining duration of the mission.
Duration	Indicates the number of events (for frequency of per event) or days (for frequency of per day) that a resource is to be used.	Per event duration should always be 1. Per Day duration of 3: Assigned quantity of resource is given for 3 days.

4.5.5 Partial Treatment

It is possible to assign fractional parameters for each capability or resource within the CRT. This instructs MEDPRAT to assign a less than full treatment effect to each condition and alters the outcome probability metrics accordingly. Insufficient data exist to estimate the effect of partially treating a condition based on a single capability or resource; therefore, the CRT working group elected to use a binary "all or nothing" approach for most parameters. The exception was where clear evidence for an intervention's efficacy relative to alternatives was present in the literature (e.g., medical literature supports varying efficacies of post-exposure emergency contraceptives, so these were assigned to corresponding options in the CRT) or where a capability was considered desirable but not necessary (musculoskeletal ultrasound for the diagnosis of fracture). An effort is underway for IMPACT 1.1 to assign partial treatment values to all capabilities in order to increase fidelity in partial weighting.

4.5.5.1 CP1 and CP2 Capabilities

CP1 was defined as representing only diagnostic capabilities while CP2 was defined as representing only treatment and reassessment capabilities. Although in clinical practice diagnosis and treatment often occur concurrently, this delineation was agreed upon for the purposes of the model because it simplified both CRT and TI derivation for IMPACT 1.0.

4.5.5.2 CP1 Duration

CP1 duration represents the time required for diagnosis of the condition. This was assigned during the CRT working group discussions. The required time for each CP1 capability was agreed on by consensus at meetings with a minimum of 3 SMEs. Standardized times for each capability were assigned and added together to generate a total duration of CP1 for each condition.

4.5.5.3 Methodology for CRT Construction

The CRTs were constructed in a stepwise fashion. Each SME in the CRT working group was assigned as the point person for a subset of the 120 original conditions. The conditions were assigned based on expertise and practice familiarity.

The point person completed a review of the literature inclusive of terrestrial professional practice guidelines to develop a list of capabilities needed to treat the best-case and worst-case definitions of each assigned condition. Considerations for the feasibility of resources (e.g., magnetic resonance imaging *vs.* ultrasound) for exploration missions included: mass and volume, necessity, current capabilities on the ISS, existing technology, and typical methods of practice in austere environments (e.g., Antarctica, ocean vessels, etc.). Based on these factors, SME consensus was reached. Future technology can be incorporated in future versions of IMPACT. Clinical creativity was also used if alternates could be considered (e.g., using a Foley catheter as a tourniquet). In an outline, necessary resources were listed with these capabilities, as were dose types, amounts, and the relevant parameters described in Section 4.5.4.

If necessary, additional SME input was sought to ensure that the capabilities discussed and resources assigned represented the best-practice guidelines as defined by actively practicing care providers, specialists, and/or astronauts. This input was incorporated into the outline.

Each outline was brought before a CRT working group meeting with a minimum of 3 SMEs present. The outline's capabilities and resources were discussed, and appropriate parameters assigned by consensus discussion and real-time literature review. Adjustments were then made to the outline and a document (CRT prose) was drafted by the point person to summarize the logic, limitations, and practice standards to be used by the CRT. CP1 duration was also agreed upon by consensus during this meeting.

The adjusted outline and draft prose were then sent for review by aerospace pharmacists who provided feedback on the pharmacy capabilities and resources the CRT working group identified. Any conflicts between the pharmacy

team recommendations and the CRT working group were resolved by discussion at subsequent CRT working group meetings.

The point person then incorporated all feedback into a finalized outline and prose which were delivered to the team lead. The team lead used this outline to generate a full CRT in Microsoft Excel™. The full CRT incorporated the appropriate structure and parameters configured for import into IMPACT-MD.

The CRT file used standardized names for capabilities and resources to represent discrete items and ensure consistency between conditions. This allows MEDPRAT to avoid double counting identical resources for an accurate reflection of all capabilities required of the simulated medical system.

The prose section of each CRT, along with the CP1 durations, were included in the CLiFF. The finalized CRT was then passed to a configuration management team for further data validation and configuration for import into IMPACT-MD.

4.5.5.4 Peer Review of Capabilities and Resources

Peer review of the CRTs was performed in stages. The initial review occurred by SME discussion of the included capabilities and resources. This stage required a minimum of 3 individuals with expertise relevant to the condition to agree on the capabilities, resources, and parameters to be included in the CRT. Any conflict was resolved through additional expertise obtained either within or from outside the CRT working group. No CRT was constructed without SME consensus on the relevant practice guidelines, adaptations, capabilities, resources, and parameters.

The second stage involved pharmacists with expertise in aerospace medicine reviewing and providing feedback on all pharmacy relevant resources and capabilities. This included medication, quantity, dose frequency, route of administration, and any pharmacy-specific issues related to the medication and its use in spaceflight. This feedback was then further reviewed by experts with relevant clinical and aerospace medicine expertise and incorporated into the CRT. Medications were flagged if they were not a part of the current exploration spaceflight medical formulary for additional pharmacist review. However, if SMEs felt that a novel medication to the formulary should be included, it was utilized within the CRT.

Finally, the prose was reviewed by a project scientist to ensure agreement with the rest of the CLiFF documentation and accuracy of the information contained within the CRTs.

4.5.5.5 CRT Internal Validation and Configuration

CRT configuration and validation were performed during the import from Microsoft Excel™ to the IMPACT-MD. This involved using a specially designed software tool to assess the CRT data structure, capability and resource names, and the associated parameters to identify errors. Any errors or conflicts were reported to the CRT working group and repaired. Minor errors such as spelling, structural changes, and parameter updates were corrected by the CRT working group lead while any substantive issues were brought back to the CRT working group, configuration management team, MEDPRAT representatives, and MedID representatives for SME discussion and consensus on the best approach.

The completed, peer reviewed, and validated files were then handed over for use by the larger IMPACT team.

4.6 QUALITY OF EVIDENCE

4.6.1 Overview

Legacy CLiFFs employed an evidence-grading schema that gave each of the evidence domains a ‘Quality of Evidence’ grade, as well as summary CLiFF grade—an average of all domains. The initial grading rubric for this updated project employed best practice Evidence-based Medicine (EBM) methodologies for strength of evidence for each piece of evidence addressing medical condition incidence, CP2 duration, RTDC, and LOCL. This original

rubric likewise incorporated an existing evidence, grading schema from two of the search databases themselves: DynaMed® and Cochrane Library©. Collectively these grading schemas were normalized to a single ordinal scale, from 0-4, with '4' being the highest level of confidence.

After the first batch of CUSOM condition searches was reviewed by the ExMC Clinical and Science Team, this approach was replaced with a new evidence grade process. While traditional academic evidence grading focuses primarily on the quality of the literature (i.e., type and size of study, participant demographics, etc.), the Level of Confidence schema adopted below expands on these considerations to also consider how closely the data represent the spaceflight environment. The following is the methodology utilized for this current evidence grade rubric.

4.6.2 Grading of Evidence (Level of Confidence) Method

Students (for the 84 CLiFFs generated by CUSOM) and ExMC editors (for the 36 CLiFFs generated by ExMC) were tasked with grading the five constituent domains of the Evidence Library [Incidence, proportion of best *vs*. worst-case scenarios, CP2 duration, RTDC, LOCL] with the rubric below:

GRADING SCALE

4 – Confident

3 – Somewhat confident

2 – Neutral

1 – Somewhat unconfident

0 – Not confident

Students and editors were prompted to consider the following questions when determining a single numerical evidence grade, with a clarifying instruction that it was "*not necessary to answer each of these questions, but consider all in crafting a narrative of 3-4 sentences on your rationale for grading*"**:**

- *How closely does the paper describe the medical condition that we have defined (relevance)?*
- *How closely does the population included resemble the astronaut population?*
- *Quality of the paper (number of subjects, methods, etc.)?*
- *How much do we trust the source of the evidence?*
- *How closely do we think that the data represents what we will see in a spaceflight environment?*
- *Other considerations?*

For conditions generated by CUSOM students, they were instructed to provide a level of confidence (LOC) grade and rationale for each of the papers identified as candidates for informing the condition incidence and best/worst-case scenario probabilities (TABLE 11). This individualization of evidence grade to each paper subsequently assisted the Clinical and Science Team editor and NASA biostatistician in ranking the evidence of individual papers to design an incidence distribution and assign the best/worst-case probability of this condition for MEDPRAT.

For the treatment and outcome domains (CP2 Duration, RTDC, LOCL), students gave a *single grade* for the *entire domain*, cumulative across all 4 variations: (TABLE 11)

- Treated best-case scenario
- Treated worst-case scenario
- Untreated best-case scenario
- Untreated worst-case scenario

For all CLiFFs, the ultimate Level of Confidence (LOC) scores assigned were approved by the ExMC editor and Peer Reviewer. Additionally, upon peer review, the Project Scientist provided an overall LOC in the peer review form.

TABLE 11 SUMMARY CLiFF LEVEL OF CONFIDENCE SCORING RUBRIC

Domain	Level of Confidence Grade
Incidence	For each paper + rationale
Best/Worst-Case Scenario Probability	For each paper + rationale
CP2 Duration	For overall domain + rationale
RTDC	For overall domain + rationale
LOCL	For overall domain + rationale

4.6.3 Maintenance of References

The EL project selected a commercial reference management software package (EndNote™)[25] to demonstrate traceability of discrete, condition-specific evidence in each CLiFF back to the original data source. EndNote™ library folders were created for each condition and reflect all papers reviewed, including stratification for the papers that were used to inform the CLiFF. These condition-specific libraries were created during the data collection phase of the project, sustained through the editing of the condition, made available to peer reviewers for consultation, and provided to IMPACT-MD for storage upon completion of the CLiFF. The database will be managed by IMPACT-MD.

5.0 EXMC REVIEW OF METHODOLOGY

5.1 EVIDENCE LIMITATIONS

No method for modeling medical events and medical system mitigation is perfect, and this system is no exception. There are several limitations to this modeling framework impacted by schedule, budget, data, and expertise constraints. While the authors of this document believe these methods yielded the most accurate model possible given the constraints above, it is necessary to acknowledge the limitations of the Evidence Library effort. It is important that users are cognizant of these limitations when analyzing the output of MEDPRAT runs. The limitations are categorized as either "general" or by the parameters to which they apply and listed in general order of importance in each section. In Section 6 additional recommendations and lessons identified are outlined.

5.1.1 General Considerations

1. Correlation of spaceflight risk to terrestrial medical literature is difficult. In addition to obvious environmental distinctions, terrestrial populations do not align well with astronauts due to spaceflight physiological alterations that may substantially change medical risk or condition incidence (often having effects that are not fully characterized). Further, astronauts are meticulously screened for medical disease with extensive preventive medicine programs developed to limit medical risk. Thus, it is challenging to identify a representative terrestrial population from which to derive appropriate risk metrics, and correlation of spaceflight risk to terrestrial medical literature is generally based on SME input and clinical acumen.

2. The model assumes independence of medical conditions. That is, one medical event maps to a single medical condition. However, it is often the case that a single medical event may lead to several different concurrent conditions (e.g., a single accident resulting in multiple fractures, chest/abdominal trauma, and sepsis). There is significant overlap between conditions in ICL 1.0. For example, cardiogenic shock has been defined to only occur within the context of a myocardial infarction. However, a separate condition,

[25] EndNote, Clarivate Analytics, https://endnote.com

acute coronary syndrome, includes myocardial infarction. Thus, for cardiogenic shock to occur, another condition, acute coronary syndrome, must occur. This overlap may lead to an overestimation in the incidence calculation. Careful selection and review of medical conditions to minimize overlap will result in an improvement in the accuracy of the model.

3. MEDPRAT currently treats each medical condition from the EL dataset as an independent occurrence. However, prior medical conditions and/or complications during treatment may increase the risk of secondary medical conditions. The current iteration of MEDPRAT is not built to model recurrence risk or treatment complication rates. This should be considered in future iterations. As a starting point, morbidity from pharmacologic or procedural management strategies have been proposed as future conditions for the ICL.

4. Accurate representation of condition incidence and outcome metrics for all conditions that have occurred in spaceflight is difficult to obtain, given the nature of spaceflight, the limited population exposure, challenges in clinical data collection, and privacy considerations. Current repositories of clinical spaceflight data, such as the LSAH database, remain limited to data that have been accurately and completely reported by crewmembers and their flight surgeons. This limitation is anticipated to be an ongoing challenge.

5. The EL dataset is limited to 119 conditions and their associated medical evidence. This number was selected to keep the initial data collection within budget and schedule constraints. While it does not capture all medical conditions anticipated in future exploration missions, it is comprised of conditions with a suspected significant likelihood of occurrence or mission consequence. Future iterations should expand the conditions and associated evidence to further define medical risk in the exploration spaceflight environment.

6. Ethical constraints for human and animal research limit the amount and quality of data available to characterize potential outcomes for untreated medical events, often requiring the EL dataset to reflect SME opinion in lieu of higher quality evidence for untreated scenarios.

7. The EL and associated CLiFFs were developed using a 210-day cis-lunar DRM. Thus, there will be inherent inaccuracies when applied to other DRMs (e.g., a Martian or asteroid mission). The incidence for several medical conditions depends on the gravitational fields encountered. These include fractures, strains/sprains, gravity-well operations, skin abrasions, and possibly venous thromboembolism and SANS. In future versions of IMPACT, separate incidence distributions for Mars and Lunar missions should be made for appropriate medical conditions.

8. There are inherent limitations and uncertainties in the IMPACT model outputs. With the exception of Total Time Lost (TTL), IMPACT 1.0 does not give the user appropriate confidence intervals on the outputs from the model which account for the level of uncertainty in the inputs. Therefore, the user is unable to discern whether the differences in metrics between competing trials are statistically significant. This is an important limitation, and more rigid criteria for determination of significance when comparing competing trials need to be developed.

9. As new treatment and diagnostic modalities become available (e.g., ultrasound-guided extracorporeal shock wave lithotripsy for nephrolithiasis), clinical duration times, RTDC, LOCL, CRT and TI will need to be modified as appropriate. This can be a time-consuming process.

10. The EL dataset is limited to medical conditions known to researchers, but there are "unknown unknowns," including the risk or incidence of conditions that have yet to occur during spaceflight. An example is the condition of venous thromboembolism. A sentinel case report[26,27] was published describing the occurrence

[26]Marshall-Goebel K, Laurie SS, Alferova IV, et al. Assessment of jugular venous blood flow stasis and thrombosis during spaceflight. JAMA Netw Open2019; 2(11): e1915011

[27]Auñón-Chancellor SM, Pattarini JM, Moll S, Sargsyan A. Venous Thrombosis during Spaceflight. N Engl J Med. 2020 Jan 2;382(1):89-90. doi: 10.1056/NEJMc1905875. PMID: 31893522.

of a deep vein thrombosis in spaceflight. This condition was not included in the iMED or IMM modeling database. It was included in the ICL 1.0 for the current effort. Insight into novel spaceflight medical conditions is provided by continued spaceflight experience and vigilance in the space medicine community. Recognition of such "new" conditions or disease processes should drive future iterations of this modeling effort.

11. There is no clinical loss of mission (LOM) metric in this dataset. While RTDC (Section Removal to Definitive Care (RTDC)), and TI (Section 3.6) will influence a LOM metric, a specific LOM metric is beyond the scope of IMPACT 1.0. Future iterations of this effort should consider defining such a parameter.

12. In many cases a discrete value was used for an input such as best case/worst case percentage, TI, and LOCL or RTDC percentages. This sometimes resulted from an editor taking the mean value of a parameter from several studies. Unfortunately, using a single number fails to capture the uncertainty inherent in the quantitative assignment of the input, leading to an over-confidence in the resulting outputs.

5.1.2 Incidence Estimation

Using terrestrial studies with large cohorts leads to tighter confidence intervals around incidence estimates than is justified. Often terrestrial data is not as reliable in predicting the spaceflight occurrence of medical conditions as spaceflight or analog evidence. However, because the number of subjects in terrestrial studies is far greater than in spaceflight datasets, the probability distributions around the incidence values are much tighter, despite the generally lower applicability of terrestrial evidence to the spaceflight environment.

1. When using multiple studies to calculate incidence, the statistical methods result in the study with the largest sample size influencing the incidence value most strongly. This is particularly true when terrestrial studies with large sample sizes are combined with spaceflight data which have small sample sizes. This led to a preference for spaceflight data over terrestrial data where it existed (as described above).

2. Under-reporting of medical conditions by the crew may occur. There are several reasons for under reporting. Mild symptoms or common conditions (e.g., headache) warranting expectant management or basic treatment may not be considered sufficiently bothersome to report or log medication use. An affected crewmember may want to minimize burden to the rest of the crew. A crewmember may consider the condition to be private or be concerned about future assignment if he/she records medical morbidity. While this underreporting may result in an underestimation of the incidence of these conditions, it is unlikely that this has a major effect on the model since most cases are subclinical. The crew will most certainly report any medical condition that affects performance or that could lead to serious medical consequences. It is not recommended that further modification of incidences be made to account for possible underreporting.

3. Until segmented mission phases are implemented, it is reasonable to confine the composite incidence calculation to a single phase that has the highest incidence. For example, most fractures were assumed to be much more likely to occur during surface operations under partial gravity conditions than during microgravity phases of flight. Therefore, the possibility of a fracture during microgravity operations was ignored (except for stress fractures related to exercise in microgravity). This method was thought to add more precision to the incidence calculation since the higher fracture incidence during surface operations is not being applied to the entire mission. It does raise the possibility for underestimation of the incidence of such conditions during microgravity phases of the mission.

4. IMPACT 1.0 is unable to distinguish between vehicles or mission phases. There can be wide differences in incidence depending on the mission phase or vehicle. A single value may not accurately represent the incidence across all mission segments.

5.1.3 Clinical Phase Duration

1. Clinical Phase duration is described fully in Section 3.5. CP2 is defined as the time period required for treatment and convalescence of a medical condition. All relapses or reoccurrences necessitating additional treatment also occur during CP2. Because CP2 applies to both the acute and convalescent stages of the condition, the range for this duration can be quite large. For many conditions it spans the entire DRM. This broad range increases uncertainty in the calculation of TTL, creates a challenge for assigning TTL, and creates the potential for the model to suggest over-resourcing medical supplies.

5.1.4 Task Impairment

TI as described within this methodology is a new metric that has not been previously validated. Future efforts may wish to seek clinical or real-world validation of this metric from an SME audience outside of the element.

1. Due to project deadlines, the initial TI calculations were blinded to EL data collection and development of other parameters in the CLiFF such as CP2 duration, RTDC and LOCL. A preliminary review of TI after completion of the CLiFFs showed a disparity between the original TI estimations and TI estimations considering these other parameters. As a result of this review, a reworked calculation of task time lost (see Section 3.6.1.5) was implemented that was felt to be more operationally faithful. Importantly, conditions with long CP2 times have the largest potential for overestimation of Task Time Lost (TTL) given that CP2 is not separated into an acute and convalescent treatment phase. Numerous conditions, especially when untreated, have durations that span the length of the DRM as they are not expected to resolve without treatment. However, TI during the acute management stage may be different than TI days, weeks, or months later, even for chronic conditions. The user should be aware of potentially large uncertainties in the TTL estimates. This uncertainty may have implications for weighting of TTL compared to RTDC and LOCL when making mission simulations using IMPACT.

2. TI accounts for time and activity lost only by the affected crewmember. There is not a metric within the dataset that accounts for the reduction in other team members' productivity while caring for the affected crewmember. Future iterations of IMPACT may wish to collect data on treatment time and secondary team care involvement for various conditions. Provider knowledge, skills, and abilities may also significantly affect this time, as could disease progression, patient outcome, or behavioral health impacts on non-patient crewmembers. Simultaneous TI of multiple crewmembers may increase risk of mission loss.

3. If a medical condition is determined to impair a Human System Task Category (HSTC), then all tasks in that HSTC are considered impaired. TI does not account for individual tasks that may be partially impaired (e.g., pain making a task slower). As an example, if a medical condition even partially affects vision (e.g., depth perception), the crewmember will be considered impaired for all tasks in which visual input is required.

4. TI represents the potential for a crewmember to have a limited ability to perform mission relevant tasks. While this is useful, it does not separately capture crewmember discomfort or delineate tasks that are impaired due to aeromedical disqualification versus physical inability to perform the task. Future efforts may wish to modify TI to represent varying levels of impairment for translation to mission success.

5. TI does not consider possible redistribution of tasks within the crew after a condition causing task impairment occurs. For example, suppose that crewmember 1 suffers a condition leading to task impairment and inability to perform Task A; however, he still can perform Task B. Crewmember 2 could be assigned to do Task A for crewmember 1 while crewmember 2 could perform Task B for crewmember 1. This would be a logical consequence of a crewmember's task impairment and would significantly reduce the overall mission TTL.

5.1.5 RTDC

The interpretation of RTDC varied widely between CLiFFs. Often, the need for hospitalization was used as a surrogate for RTDC. However, the onboard medical capabilities might fulfill this role (e.g., need for continuous monitoring, IV fluids, IV/IM pain control, IV antibiotics, etc.). Thus, lack of an onboard capability to treat a condition when lack of treatment will result in a significant disability is a better definition for RTDC. RTDC probabilities may need to be refined in the context of the medical system and onboard crew Knowledge, Skills, and Abilities (KSAs). A comprehensive review of these shortcomings has been completed and will be implemented for IMPACT 1.1.

1. The ICL 1.0 conditions were reviewed by SMEs from the EL Team prior to the rapid systematic review. Some conditions were judged to require RTDC with 100% probability by the SMEs. These were annotated and RTDC literature searches were not performed for these conditions. In retrospect, this process should be done for new conditions after the most up to date evidence has been evaluated during the review process. Standard practice and therapeutics may have changed. New capabilities may also be available onboard that could increase the level of care provided during spaceflight.

5.1.6 CRT

For the purposes of modeling, resources and resource bundles with equivalencies indicated are deemed 100% effective unless there is documented evidence proving otherwise. Primacy is only used to indicate the preferred resource or bundle. In future iterations of IMPACT, researchers will consider how to document non-equivalent or inferior resources to make the CRT dataset more comparable to terrestrial medical systems.

CRTs in their current form require all capabilities (unless listed as zero necessity) to be present for a condition to be treated. If a capability is not present, the condition reverts to the untreated state. This implies that all capabilities affect all outcomes which may not be clinically realistic. For example, pain medications may reduce TI but are unlikely to alter LOCL for a given condition. In future versions of IMPACT, a hierarchy of capabilities may be implemented to address this limitation, such as “preventive” capabilities affecting only incidence, “comfort” capabilities affecting only TI, and “life-saving” capabilities affecting only LOCL. For IMPACT 1.1, work is being done by SME clinicians to weight the efficacy of all capabilities used in each condition. This will allow partial weighting of resources per condition and improve the fidelity of the IMPACT Evidence Library.

1. The effects of decreasing potency of medications should be considered as they approach their expiration date during spaceflight. Depending on the shelf life of pharmaceuticals needed to treat a certain medical condition, the condition may change from “treated” to “untreated” as the mission progresses. Importantly, the effects of space radiation on shelf life are also not fully understood.

2. Most treatment pathways and associated outcomes within the EL dataset are rooted in terrestrial knowledge. The treatment of certain conditions in spaceflight could be affected by human physiology, disease progression, human-pathogen interaction, microbiome shifts, and medication stability. Additionally, some medical interventions are more difficult and time-consuming to perform in space. These are gaps yet to be addressed in the Human Research Roadmap and thus could not be included in IMPACT 1.0.

3. The CRT dataset assumes there is no real-time communication with the ground and no ability to resupply. Different mission phases may use different vehicles and different medical resources. IMPACT 1.0 does not distinguish between conditions that can be treated only in some mission phases or when an escalation between mission phases is mandated to reliably treat a condition. Further, it does not consider the impact of a time delay on treatment outcome. Future data collection efforts, in partnership with modelers, could provide medical evidence to help address these limitations.

4. The CRTs employed the terrestrial standard of care filtered through the lens of what would be practical in a spaceflight environment. Resources were only included if they were likely to have a substantial outcome

on a particular condition, assist in diagnosis by eliminating mimicking conditions, or substantially increase a patient's function or quality of life.

5. Resource scoping assumes conditions occur a single time during the mission. While MEDPRAT simulations can inform the medical system to constrain resources for events to occur with recurrence, the possibility exists that a necessary diagnostic or management resource may not be available. This is also of concern with shared resources between conditions.

6. Occasionally, resources were creatively inserted by physician team members for use when traditional resources were unavailable (e.g., using a Foley catheter as a tourniquet). This was done inconsistently, and there are likely many more resources that could be used with off-label diagnostic or therapeutic functionality.

7. A Scope of Practice code was recorded for each capability within the CRTs with the future intent to factor KSAs of providers into IMPACT. Scope of Practice code is not yet functional in IMPACT 1.0 but planned to be used in future iterations. It is unknown whether the Scope of Practice code alone will deliver the distinction in KSAs to add the desired fidelity to IMPACT risk assessments.

This list outlines the most significant limitations that the EL team has identified at the time this document was prepared and attempts to convey to the user that there are inherent uncertainties within the model. The user should avoid using the model in applications for which it was not designed.

5.2 ADVANCEMENTS BEYOND INTEGRATED MEDICAL MODEL DATASET

Methods employed to collect and document the EL dataset were built upon the foundational work of the IMM and iMED over its lifetime. Strengths and lessons learned from the IMM, communicated via an external, independent methodology review of the tool were used to inform EL methods to help ensure adequacy and accuracy of the dataset upon project completion.[28]

5.2.1 Building on IMM Dataset Strengths

Strengths identified in the IMM review that were applied to this project included:

- Use of epidemiological and statistical methods for measuring incidence and quantification of impact on defined outcomes.

- Use of transparent, comprehensive methodology to identify medical conditions relevant for the exploration spaceflight environment, including conditions that have occurred in flight and those that could be of concern.

- Use of methods and tools to communicate medical evidence that are adaptable and scalable.

5.2.2 Addressing IMM Dataset Critiques

Critiques in the IMM external review focused on lapses in documentation and configuration management, team communication issues, and challenged the scientific rigor applied to methods employed to populate and review the dataset. The EL team has invested effort early in the project to ensure this feedback was considered and implemented within project and schedule constraints. This has included:

[28]IMM Model Version 4.0 Review Board. IMM External Independent Review Board Final Report, Appendix C IMM Methodology Review (#2) Review Summary/RFAs/Responses. (2016). Unpublished project document. p 134-140.

- Development of documentation templates and configuration management tools and processes tosupport reproducibility of search methodologies and limit the risk of inadvertent data changes orfile corruption.
- Inclusion of interdisciplinary expertise to enhance data collection quality, and internal peer review including library science, epidemiology, biostatistics, and evidence-based medicine experts.
- Organizational and business infrastructure tools to support team communication and data reporting.
- Processes to demonstrate peer review along the data collection and reporting continuum.
- Establishment of a Medical Database Control Board to manage approval and configuration management of all changes to the database.

5.2.3 Dataset Enhancements Enabling Expanded Trade Space Assessment

Additionally, enhancements were made to expand the dataset to make it more applicable to the exploration spaceflight environment and ExMC's desire to have an enhanced ability to assess the engineering/clinical trade space. These enhancements include:

- Expansion of the condition list from 100 to 119 conditions, taking into consideration new exposures associated with planetary/surface exploration.
- The DRM was changed from ISS/LEO to 210-day cis-lunar, which is more applicable to exploration.
- Inclusion of resources beyond the ISS medical kit.
- Redefinition of conditions and best-case/worst-case scenarios to make a more realistic connection with capabilities and resources required to diagnose and treat, as well as making definitions more closely aligned with reported evidence used for risk estimation.
- Development of a methodology to characterize crew impairment caused by medical conditions that is directly applicable to spaceflight tasks, as opposed to adapting terrestrial disability data.
- Mapping of conditions to capabilities and resources needed for diagnosis and treatment that allows for assessment of alternate options.
- Higher fidelity incidence distributions for medical conditions made possible by collaboration between biostatistician support to clinicians to best characterize incidence and outcomes data, and support to MEDPRAT modelers to suggest coding updates to accommodate use of these distributions.
- Bundling of resources to reflect true grouping of resources that must be used together to achieve the full effect of 'treatment' in a simulation.
- Equivalencies for medical resources beyond pharmacy to better reflect clinician creativity opportunities when practicing medicine in low resource, austere environments and to enhance trade space capabilities for medical system optimization tools.

6.0 LESSONS IDENTIFIED AND RECOMMENDATIONS

6.1 GENERAL LESSONS IDENTIFIED

1. An attempt should be made to perform components of the evidence collection for CLiFF development as concurrently as possible. This increases accuracy and mitigates the loss of corporate knowledge. CRT and TI development should include Clinical and Science Team staff who were involved in the CLiFF creation and data collection for the associated condition. This enables accurate determination of TI and CRT in an iterative process that can correct and modify data processes that were accomplished upstream. A recommended sequence of Evidence Library development for future medical conditions is:
    a. Recommend new medical condition.
    b. Gather evidence about the condition.
    c. Confirm/adjust condition definitions based on literature review.
    d. Based on evidence, decide on the best-case and worst-case probability.
    e. Complete the CLiFF (incidence, best-case/worst-case scenario probability, CP2 duration, RTDC and LOCL) using the sequential process described in Section 3.2.
    f. Complete the CRT.
    g. Complete TI using the CP2 duration and CLiFF inputs listed above.
    h. As the process proceeds the developers should evaluate previous steps for accuracy and modify calculations as indicated, consistent with an 'Agile philosophy.'
2. The time required to develop the CLiFFs was underestimated. Depending on the medical condition, editors developing CLiFFs without CUSOM assistance could spend up to 50 hours gathering evidence, attending meetings to discuss the available data, interfacing with biostatisticians, and going through an iterative review process. Some conditions required interfacing with engineering or PRA experts; this increased the time necessary for evidence collection. This is particularly true for future additions to the medical condition list as there will probably not be a supporting team (such as CUSOM) to help the editors make a draft CLiFF version. It is recommended that time assigned to this effort should be calculated and allocated mindfully in the future.
3. It is recommended to include an individual with spaceflight experience (i.e., someone who has flown in space) on the team. This adds a useful perspective in the review and evidence-gathering process. An astronaut-physician would be an ideal addition to the team, but a non-medical crewmember could also provide valuable input.
4. Advanced planning across teams involved in IMPACT (MedID, IMPACT-MD, MEDPRAT, Pharmacy, and EL) before starting updates and CLiFF development is critical. This is recommended to streamline future versions of IMPACT and minimize re-work. If new medical conditions, medical capabilities, or MEDPRAT features are added, all components of the IMPACT project should be aware of the implications of those changes to their work and express their concerns to leadership prior to implementation. For example, IMPACT-MD was not involved in the creation of the CLiFF template resulting in added work to process the CLiFFs.
5. When EL definitions, methods, or approaches change (even in seemingly minor ways), there is a ripple effect on IMPACT-MD, MEDPRAT, MedID, and pharmacy. It is recommended that all changes, no matter how small, be coordinated with the entire IMPACT team, so that all groups are not expending resources using outdated information. Improving communications and making all information available to team members are key strategies to eliminate wasted effort and improve the accuracy of the model.
6. Computer science/data architecture support for the Clinical and Science Team is needed for future versions of IMPACT. The initial components of the CLiFFs, populated by the Clinical and Science Team clinicians, were all Microsoft Excel™ documents. The CLiFF document with incidence, best-case/worst-case probability, CP2 duration, RTDC and LOCL resided in one Excel™ spreadsheet. It included the TI

values for the condition, but all TI values were generated in a separate Excel™ spreadsheet. Similarly, the prose explaining the CRT was included in the CLiFF document, but a separate spreadsheet provided the CRT data. These Excel™ inputs now reside in IMPACT-MD which has been modified to accept these data. In the future, using Excel™ as an intermediary step will be unnecessary and data will be recorded initially in IMPACT-MD. A data scientist can now create, manage, and assist in the storage of data using the IMPACT-MD interface, allowing the clinicians on the Clinical and Science Team to focus their efforts solely on evidence collection. This will streamline these processes, reduce human error, and allow continual, real-time testing and validation during development.

6.2 MEDICAL CONDITION LIST

If a crewmember becomes seriously ill, injured, or dies during the course of a mission, the assumed independence of medical conditions in the model does not account for the potential increase in behavioral health-related conditions affecting other crewmembers. Significant medical events are often stressful for both the patient and providers. This is especially true if care provision is not the primary duty of the provider, as would be the case on exploration missions. It is recommended that future versions of IMPACT consider such increases in psychological conditions following medical events. If a model end-state is created to address the psychological stressors of spaceflight, it should also be able to account for the effect of unexpected emergencies (medical and otherwise) on both the patient and non-patient crewmembers.

Common side effects of frequently used pharmaceuticals have not been considered in the medical condition list. As a more extensive formulary will be carried onboard during exploration missions than was previously manifested, it is likely that more undesirable medication side effects will be encountered. Serious side effects from medications are recommended to be considered for inclusion in the medical condition list, along with appropriate treatment resourcing. This is also true for complications of diagnostic or therapeutic procedures.

Hematologic and metabolic analysis diagnostic tools are being actively investigated for use in exploration missions. While these are excellent for non-specific complaints (e.g., fatigue), they pose a dilemma when abnormal values are encountered. For example, thrombocytopenia, anemia, leukocytosis/penia, eosinophilia, hyperkalemia, hyponatremia, acidemia, elevated transaminases, signs of biliary obstruction, acute renal failure, proteinuria, positive hemoccult, hypo/hyperthyroidism might be incidentally found during routine testing. It is recommended that consideration be given to adding some of the more common and consequential of these incidental diagnostic findings to the ICL.

6.3 INCIDENCE

Lunar and Martian missions may differ significantly in terms of vehicles and mission profiles. When estimating the incidence of medical conditions, it is better to use anticipated data for exploration vehicles or mission profiles than to use outdated data from vehicles or missions in low earth orbit (LEO). An example would be using historical data from ISS dealing with environmental conditions that will be non-applicable to exploration missions. In some cases, data for exploration missions is not available and may only be projected or described in engineering or PRA analyses.

Pharmacologic usage may be a more precise source of incidence data than astronaut reporting for a number of minor conditions such as insomnia, upper respiratory tract infections, nasal congestion, and headache. Accurate accounting of astronaut medication usage, including timestamping, is recommended to be actively pursued. When available, pharmacologic usage data is likely to provide the most accurate incidence estimations and should be used.

6.4 BEST-CASE AND WORST-CASE DEFINITIONS

Best-case (BC)/worst-case (WC) scenario definitions are recommended to be determined after a review of the available evidence. The authors should ensure that there is applicable evidence to support the definitions and the BC/WC probability. If no evidence exists, the BC/WC definitions for the condition should be changed to utilize evidence that more strongly supports calculation of CLiFF parameters.

Where uncertainty exists in the BC/WC probability, it is recommended to use a range of values rather than to use an estimated midpoint. MEDPRAT can convert a range into a distribution which reflects the uncertainty inherent in the estimation of the BC/WC probability.

6.5 TASK IMPAIRMENT

Currently, TI is represented with discrete values for the BC/WC treated and untreated scenarios for CP2 and CP3. The CP2 duration for some conditions has a wide range, from a few hours to the entire length of the mission. This affects the TTL calculation (TI x duration) and may result in a large uncertainty band around the estimation of TTL. While using a range for TI% will likely increase the confidence intervals associated with the calculation, it more accurately reflects the uncertainty associated with assignment of a TI% value.

When tasks for Artemis missions are known, it is recommended that they be used to compute TI instead of the Mars Task List.

Using mission phases to customize TI is recommended in the future.

It is recommended that the TI of the crew involved in the treatment of an ill or injured astronaut (e.g., the CMO) be calculated to more accurately estimate the mission impact of a medical event.

6.6 CRT

Time invested in process development through pilot projects and meetings with all involved parties will greatly improve efficiency and is worth the investment. Initial development of CRTs and the design of IMPACT-MD tools were done without sufficient coordination between groups (Evidence Library, iMED, IMPACT-MD, Pharmacy, and MEDPRAT). By ensuring that all parties are aware of the choices made, the limitations accepted, and the necessary assumptions/workarounds employed rework can be avoided. While process development may result in scant progress initially, the ultimate outcome is an improvement in efficiency and the quality of deliverables.

Communication between all involved groups is essential. It is impossible to construct a functional multidisciplinary project without acknowledging the needs of all disciplines. In the CLiFF and CRT efforts, lack of coordination between teams responsible for data collection, organization, and end-users, resulted in increased workload, stress, and lost time. It is recommended in future efforts, that representatives from each team should be involved in the process development stage as early as possible and hold coordination meetings on a regular basis.

Consensus meetings can streamline review. The CRT effort derived benefit from integrating review into the developmental process. Assigning a single individual to collect initial data and lead team discussion and review saved time and effort for other members of the CRT working group, allowing them to focus efforts on their assigned tasks. In future iterations of IMPACT, a similar process is recommended.

The CRT effort was hindered by input received from teams or individuals outside the CRT working group who were not fully cognizant of the methods and processes being used. It is critical that development and implementation are not performed in isolation. It is recommended that all parties involved in the CRT process should have regular communication and establish mechanisms to solve problems synchronously and spend sufficient time together to understand the full scope of the project.

6.7 EL INTERFACE WITH MEDPRAT, MEDID, AND IMPACT-MD

It is recommended to keep user manuals and methods documents up to date. If it is not possible to make formal policies or modifications in methods documents, these changes should be widely published and communicated to all members of the team.

The modeling effort and evidence collection process should proceed alongside the development of IMPACT. It is recommended to synchronize these efforts. As changes to the model are made and questions arise, these should be addressed promptly. All team members should be informed of the outcomes of such discussions to avoid rework.

Meetings scheduled at regular intervals including MEDPRAT, MedID, IMPACT-MD, Pharmacy, and EL (The Clinical and Science Team) are recommended to assist in coordination and communication for future versions of IMPACT.

Due to their complexity compared to the resources from IMM, CRTs required substantial programming changes in MedID and IMPACT-MD. The import process to IMPACT-MD was tedious because, like all components of the CLiFFs, CRTs were built in Excel™. The import process could take as much as 2 weeks and was necessary any time changes were made to the CRTs. Although proportionately there were not many human errors in the CRT Excel™ spreadsheets, due to the sheer number of fields associated with the CRTs, these errors required substantial time to correct. Data needed to be audited for errors and re-imported. This is an important lesson identified as work goes forward. Investment in software that can help eliminate errors and automate processes is well spent.

6.8 ADMINISTRATIVE AND SOFTWARE TOOLS

Common standards and ontologies used to communicate data and information associated with medical condition definitions, symptomology, and diagnosis and treatments were not used in the EL dataset. Future update efforts should consider ways to communicate data that better support interoperability and integration with clinical decision support systems.

EndNote™ files cannot currently be updated by the ExMC editors. The files are not stored on the cloud, so when references are added to a CLiFF by an editor, they cannot be added to the baseline EndNote™ file. It is recommended that software be utilized that enables remote users to add references to the list.

APPENDICES

APPENDIX A REFERENCE DOCUMENTATION

The following documents contain supplemental information and provide guidance for content containedwithin this Evidence Library Methods document. These documents may or may not be specifically citedwithin the text of this document.

DocumentNumber	Document Owner	Title Link (if available)
CCMP-MEDPRAT- DOC-002	CCMP, Human Research Program	MEDPRAT User's Manual
CCMP-MEDPRAT- DOC-001	CCMP, Human Research Program	MEDPRAT Concepts / Capabilities /Functional Requirements
CCMP-MEDPRAT- DOC-003	CCMP, Human Research Program	MEDPRAT Software Design Document
HRP-47077	IMM Project, Crew Health & Safety	Integrated Medical Model ConceptualModel Document
HRP-48020	ExMC Element, Human Research Program	IMPACT Concept of Operations
iMED LockDown 68	IMM Project, Crew Health & Safety	iMED Database
IMM-GEN 309, Rev 1	IMM Project, Crew Health & Safety	IMM Medical Conditions List
IMM-GEN-302	IMM Project, Crew Health & Safety	IMM Clinical Finding Forms Overview
IMPACT-REQ-0007	ExMC Element, Human Research Program	Project Technical Requirements Specification (PTRS) for the IMPACT ToolSuite
IMPACT-CONOPS-0032	ExMC Element, Human Research Program	IMPACT-Medical Database Concept ofOperations
IMPACT-DOC- 004	ExMC Element, Human Research Program	IMPACT User’s Manual
IMPACT-PLN- 001	ExMC Element, Human Research Program	IMPACT Project Plan
IMPACT-SDD- 0009	ExMC Element, Human Research Program	IMPACT Software design document
JSC-65722	ExMC Element, Human Research Program	Exploration Medical Condition List, Rev C
NASA/CR-2018-220043	Human Factors and Behavioral Performance Element, Human Performance Program	Human Exploration of Mars: Preliminary Lists of Crew Tasks
NASA-STD- 7009A w CHANGE 1	NASA Headquarters	NASA Technical Standard: Standard forModels and Simulations

DocumentNumber	Document Owner	Title Link (if available)
Unpublished	ExMC Element, Human Research Program	Evidence Library Pilot Project Final Report -EL PP Toxic Exposures and InjuriesCondition List -EL PP REP Study Condition List -EL PP Spaceflight Condition List
Unpublished	Artemis Program Medical Officer, SpaceMedicine Operations	Draft: Artemis Phase I: Functional MedicalConcept of Operations Condition List
Unpublished	EVA Incapacitated Crew Rescue WorkingGroup (SA)	Draft: Lunar EVA Incapacitation ConditionList
Unpublished	ExMC, Human Research Program	Evidence Library Team Condition List

APPENDIX B EXAMPLES (ICL35 AND ICL97) OF CLINICAL DATA FOR IMPORT INTO IMPACT-MD (CLIFF TAB 9B)

ICL35 DIVERTICULITIS-ACUTE CLiFF
OVERVIEW
Wilkins et al, 2013 provides the following overview of acute diverticulitis terrestrially: "Uncomplicated diverticulitis is localized diverticular inflammation, whereas complicated diverticulitis is diverticular inflammation associated with an abscess, phlegmon, fistula, obstruction, bleeding, or perforation. Patients with acute diverticulitis may present with left lower quadrant pain, tenderness, abdominal distention, and fever. Other symptoms may include anorexia, constipation, nausea, diarrhea, and dysuria. Initial laboratory studies include a complete blood count, basic metabolic panel, urinalysis, and measurement of C-reactive protein. Computed tomography, the most commonly performed imaging test, is useful to establish the diagnosis and the extent and severity of disease, and to exclude complications in selected patients. Colonoscopy is recommended four to six weeks after resolution of symptoms for patients with complicated disease or for another indication, such as age-appropriate screening. In mild, uncomplicated diverticulitis, antibiotics do not accelerate recovery, or prevent complications or recurrences. Hospitalization should be considered if patients have signs of peritonitis or there is suspicion of complicated diverticulitis. Inpatient management includes intravenous fluid resuscitation and intravenous antibiotics. Patients with a localized abscess may be candidates for computed tomography–guided percutaneous drainage. Fifteen to 30 percent of patients admitted with acute diverticulitis require surgical intervention during that admission. Laparoscopic surgery results in a shorter length of stay, fewer complications, and lower in-hospital mortality compared with open colectomy. The decision to proceed to surgery in patients with recurrent diverticulitis should be individualized and based on patient preference, comorbidities, and lifestyle. Interventions to prevent recurrences of diverticulitis include increased intake of dietary fiber, exercise, cessation of smoking, and, in persons with a body mass index of 30 kg per m or higher, weight loss."
INCIDENCE DATA INCLUDED IN MODEL
The model imports the following incidence information from the MEDPRAT Evidence Library Database: incidence data category, space adaption status, EVA status, incidence data type, incidence and occurrence distribution data and incidence data characteristics. *Data category* defines the type of data available for incidence calculations (i.e., raw data vs. adjusted data). *Space adaptation* identifies medical events that where onset occurs in the first 5-7 days of flight and does not reoccur. EVA-related incidence values identify medical events that occur only during an EVA. Incidence values types vary by data category and define the number of medical events per person-year (rates) or medical events per person at-risk (proportion) for each medical condition. Incidence values can be modified by crew characteristics such as gender sex and certain crew medical history characteristics. Modifying characteristics are noted below and incidence values are listed individually for each characteristic. Distributions are assigned to medical events incidence values and occurrences in the model. For each crewmember in a given trial, the incidence and number of occurrences of each medical condition are randomly selected from these probability distributions. Detailed descriptions of the distributions are included in the MEDPRAT Technical Description Document.
INCIDENCE DATA
SPACEFLIGHT LITERATURE
No cases of diverticulitis during spaceflight have been observed/recorded to date in the literature. Antonsen et al, 2021, projected 156.45 incidents (130-182, 95% Confidence Interval) of diverticulitis during a simulated Accelerated Mars Mission (AMM) scenario with 426 days total trip time, and 603.3 (482-673, 95% Confidence Interval) of diverticulitis during a Standard Mars Mission scenario with 923 days total trip time. Both mission scenarios included 4 crewmembers, 2 male and 2 female. The AMM scenario assumed 60 surface EVAs in pairs. The SMM assumed 401 4-person EVAs. Both scenarios assumed solar maximum radiation levels. This reference was not used to inform the incidence for this CLiFF because the data driving the simulation was the terrestrial data included in the IMM. This CLiFF will update that terrestrial data.
ANALOG LITERATURE

No analog studies for diverticulitis were identified in the literature.

TERRESTRIAL LITERATURE

The majority of data available on incidence of diverticulitis is from terrestrial retrospective epidemiological reports. Overall, these indicate an increasing incidence of diverticulitis among US citizens over time, as well as an expected increase in incidence with age. There is also a slightly higher incidence among women (Bollom et al, 2017; Bharucha et al, 2015). Cao et al, 2018 and Strate et al, 2011 are both large prospective cohort studies of male subjects only from the Health Professionals Follow-up Study, examining the relationship of dietary meat intake and NSAID use, respectively, to diverticulitis. Subjects were 40-75 years of age. These references were not used to inform the incidence for this CLiFF since they exclude females. Bollom et al, 2017 is a large retrospective study utilizing the National Emergency Department Sample (NEDS) database and therefore only captures diverticulitis diagnosis that presented to the emergency department. It includes females and stratifies the incidence by age and sex. However, it only includes diverticulitis diagnoses that were made in the Emergency Department. Many cases of diverticulitis (particularly uncomplicated cases) are managed on an outpatient basis. Thus, this is anticipated to underestimate the true incidence of diverticulitis. Bharucha et al, 2015 is a retrospective study from the Rochester Epidemiology Projected database, including 3,222 diverticulitis patients in Olmstead County, MN over a 27 year period (1980-2007). It includes approximately 50% females and stratifies the results by age and gender. This includes outpatient, emergency department, and inpatient care. Notably, as is the case with all of the terrestrial studies considered, this incidence will overestimate the risk of diverticulitis in the astronaut corps since known risk factors for diverticulitis include sedentary lifestyle, obesity, smoking, and overuse of NSAIDs (all less common in the astronaut cohort). Recurrent cases were also included, which is also anticipated to overestimate the incidence for the astronaut corps as it is assumed that astronauts would either have definitive surgical intervention or not be qualified for spaceflight. Despite this, Bharucha et al, 2015 was felt to be the most representative data available for the incidence for this condition, once age-restricted to match the age of the astronaut corps. Thus, this study was used to inform the incidence for this CLiFF.

TABLE 1. OVERALL INCIDENCE SUMMARY

Incidence	**Males:** Mean 0.001616 SD 6.628E-5 **Females:** Mean 0.00183 SD 5.703E-5	*Table 1 Caption.* Data from the terrestrial Rochester Epidemiological Project, Temporal Trends in the Incidence and Natural History of Diverticulitis: A Population-Based Study was used to inform the incidence for this CLiFF (Bharucha et al, 2015). Since the rate increased over time, we used estimates from the most recent period, 2000-2007. US Census data were used for population counts as well as age and sex distribution in Olmstead County during this period. The Bayesian posterior distributions for the age-adjusted (to flown astronauts) incidence rates given the terrestrial study, under uninformative priors is Gamma(shape=594.45, rate=367854.7) for males with mean 0.001616 and SD 6.628E-5, and Gamma(shape=430.29, rate=363729.1) for females with mean 0.00183 and SD 5.703E-5.

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 2 Caption.*
Antonsen et al, 2021	Spaceflight	2	Antonsen et al, 2021 provides a simulation-based projected incidence of diverticulitis during accelerated & standard-length Mars Missions. This was done using IMM. Cao et al, 2018 and Strate et al, 2011 are both large prospective cohort studies of male subjects only from the Health Professionals Follow-up Study, examining the relationship of dietary meat intake and NSAID use, respectively, to diverticulitis. Subjects were 40-75 years of age. Bollom et al, 2017 is a large retrospective study utilizing the National Emergency Department Sample (NEDS) database and therefore only captures diverticulitis diagnosis that presented to the emergency department. It, however, includes females. Bharucha et al, 2015 is a retrospective study from the Rochester Epidemiology Projected database, including 3,222 diverticulitis patients in Olmstead
Cao et al, 2018	Terrestrial	1	
Bollom et al, 2017	Terrestrial	2	
Bharucha et al, 2015	Terrestrial	3	
Strate et al, 2011	Terrestrial	1	

			County, MN. It includes approximately 50% females and stratifies the results by age and gender.

CREWMEMBER SELECTION/PREVENTION

DISQUALIFYING CONDITIONS

Refer to Medical Evaluation Documents (MED) Volume A, Medical Standards for ISS Crewmembers, International Space Station Program, Rev 3.4 (2016).

PREFLIGHT PREVENTIVE MEASURES

There are no specific pre-flight preventive measures to prevent diverticulitis. Crewmembers are typically very physically active and do not smoke, decreasing their risk for diverticulitis.

BEST CASE SCENARIO DEFINITION

An uncomplicated case of diverticulitis that is self-limited or responds to oral or IV antibiotics.

WORST CASE SCENARIO DEFINITION

A complicated case of diverticulitis (i.e., abscess, perforation, fistula, obstruction), requiring IV antibiotics and/or percutaneous or surgical intervention.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

The American Gastroenterological Association (AGA) Institute Guideline on the Management of Acute Diverticulitis reports that 15% of diverticulitis diagnoses are complicated 15%, defined as an abscess, perforation, fistula, or colonic obstruction (Stollman et al, 2015). This matches the worst-case scenario complicated diverticulitis parameters, but the worst-case scenario also includes "requiring IV antibiotics." The AGA recommends that antibiotics should be used selectively, rather than routinely, in patients with acute uncomplicated diverticulitis (Conditional recommendation, low quality of evidence). Despite this, the 15% value may be an underestimate of our worst-case scenario due to the inclusion of IV antibiotics in our worst-case scenario definition. Stollman and Raskin, 1999 reports that 15-30% of diverticulitis cases require surgical intervention during their hospital admission. Bharucha et al, 2015 in a retrospective study of 3,222 patients over 27 years from 1980-2007, reported 12% (386/3,222) of patients with diverticulitis experienced 1 or more complications, defined as pericolic abscess, peritonitis, obstruction, fistula, septicemia, bacteremia and/or stricture. 250 of these patients with complications required surgery. An additional 204 patients required surgery in this study. (Total of 14% - 454/3,222 required surgery). Based on the aforementioned studies, a range of worst-case probability from 12-30% was assigned and therefore the best-case scenario probability was assigned 70-88%.

TABLE 3. BEST/WORST CASE PROBABILITY LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 3 Caption.*
Bharucha et al, 2015	Terrestrial	3	Bharucha et al, 2015 is a retrospective study from the Rochester Epidemiology Projected database, including 3,222 diverticulitis patients in Olmstead County, MN from 1980-2007. Of the 386 patients with complicated disease, 63% were 60 or older, 31% were 40-59 yo, and 7% were <40 yo. Stollman and Raskin, 1999 is an American Academy of Gastroenterology Practice Guidelines for diverticulitis reporting specifically on need for surgical intervention, whereas Stollman et al, 2015 is a more recent management guideline from the American Gastroenterology Association (AGA) that reports complicated cases of diverticulitis, not limited to surgical cases.
Stollman and Raskin, 1999	Terrestrial	2	
Stollman et al, 2015	Terrestrial	3	

TABLE 4. CLiFF TREATMENT & OUTCOME TABLE BY CLINICAL PHASE

Case Scenario	*Incidence*	*Condition Probability* ^	*CP1: Diagnosis*		*CP2: Treatment*			*CP3: Condition End State*				
			TI%	*Duration*	*TI%*	*Duration*		*TI%*	*RTDC*		*LOCL*	
			Preset	Preset	Preset	Min	Max	Preset	Min %	Max %	Min %	Max %
Treated Best Case (TBC)	Males: Mean 0.001616 SD 6.628E-5 Females: Mean 0.00183 SD 5.703E-5	70-88	100%	1.75	30.614	48	98.4	0	0	6	0	0.4
Treated Worst Case (TWC)		12-30	100%	1.75	100	72	360	0	5.1	18.5	3.5	10.1
Untreated Best Case (UTBC)	*N/A*	*N/A*	*N/A*	1.75	33.883	72	840	0	4.6	17.6	0	1.1
Untreated Worst Case (UTWC)	*N/A*	*N/A*	*N/A*	1.75	100	72	8856	100	55	98	26	100

TABLE 4 KEY

Incidence: The same incidence will be used for both TBC and TWC. For EVA conditions: events per EVA (events/EVA). For space adaptation conditions: events per person (events/person). For non-spaceflight conditions: events per person year (events/py).

^Condition Probability: The probability that CLiFF condition progresses to a worst-case scenario. Best case scenario: 100%-Worst Case.

Clinical Phase General Comments:

- TI% = Task Impairment %. Task Impairment is the % of tasks that the crewmember is incapable of performing without impairment secondary to the medical condition.
- Durations are defined in hours.
- Removal to Definitive Care (RTDC): The probability the entire crew aborts the mission and returns to earth. This is considered as a condition end state result if any of the following criteria are met: 1) the potential for LOCL, 2) potential for significant permanent task impairment, or 3) potential for intractable pain.
- Loss of Crew Life (LOCL): The probability of death of affected crewmember due to medical condition.

Clinical Phase 1: Initial Assessment and Diagnosis

- Covers only the initial assessment and diagnosis of the affected crewmember to define his or her medical condition. While the affected crewmember is being assessed, he or she is not able to perform any assigned tasks, thus Task Impairment (TI) during this phase is considered 100%. In the untreated case, there is no diagnosis performed, therefore Task Impairment and Duration will always be “not applicable."

Clinical Phase 2: Stabilization, Treatment, and Convalescence

- The affected crewmember is receiving any appropriate initial or follow-on treatment for his or her medical condition to allow the crewmember to recover as much as he or she is able to recover in the spaceflight environment. Clinical phase 2 also encompasses relapses or recurrences of the same original medical condition in Clinical Phase 1. The duration of Clinical Phase 2 is expressed as minimum and maximum hours.

Clinical Phase 3: Condition End State

- Reached once the affected crewmember has recovered from the medical condition as much as he or she is able to recover in the spaceflight environment amongst treated and untreated best and worst-case scenarios. This may or may not be recovery from the given medical condition to the full extent possible. If this “recovered” state results in Removal to Definitive Care (RTDC) or Loss of Crew Life (LOCL) this will be noted in the condition end state results.

SCENARIO OVERVIEW COMMENTS

The general clinical approach to diverticulitis is to classify it as complicated vs. uncomplicated. If uncomplicated (not requiring surgical intervention, abscess, fistula, obstruction, perforation, etc.), the standard clinical practice is to treat supportively with or without a course of oral antibiotics. The data for outcomes in uncomplicated diverticulitis suggest that oral antibiotics are often not necessary, and the condition often self-resolves. In spaceflight, a more aggressive approach with antibiotics may be preferred. The RTDC surrogate initially selected for all scenarios was the requirement for surgery. However, this does not work well for the best-case scenario because requiring surgery forces a worst-case scenario based on the scenario definitions. Therefore, the requirement for hospitalization was used as an RTDC surrogate for the best-case scenarios and the requirement for surgical intervention was used as the RTDC surrogate for worst-case scenarios. See detailed comments for each scenario below.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

The duration is based on data from a review article from the American Academy of Family Physicians (2-4 days for resolution of acute uncomplicated diverticulitis) (Wilkins et al, 2013), and Shabanzadeh and Wille-Jørgensen, 2012 who reported an average resolution of leukocytosis in acute uncomplicated diverticulitis of between 2.5-4.1 day. Thus, the duration was assigned a range of 2-4.1 days (48-98.4 hours). In a retrospective cohort study of 693 patients (54% female, average age 58.5yo) from the Kaiser Permanente southern California database, 2006-2007, Etzioni et al. report 6% of patients with acute uncomplicated diverticulitis failed outpatient treatment, requiring hospitalization. Thus, the RTDC probability was assigned a range of 0-6%. Daniels et al, 2016, in a multi-center randomized controlled trial of CT-proven primary acute uncomplicated, left-sided diverticulitis in the Netherlands, comparing antibiotic treatment to no antibiotic treatment reported a mortality of 0.4% in the treatment arm. Therefore, the LOCL probability for this scenario was assigned a range of 0-0.4%.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

The duration for this scenario was assigned a range of 72-360 hours. The minimum duration of 72 hours, based on the average length of time patients have symptoms of uncomplicated diverticulitis before presenting to the hospital, from the best-case scenario (Jaung et al, 2021) will be used as the minimum duration in this scenario as well since no data was found indicating the length of time that patients have symptoms of complicated diverticulitis prior to presenting to the hospital. In a Cochrane Review meta-analysis, the averaged duration of hospital stay for complicated diverticulitis requiring open surgical resection was 7.9 days (Abraha et al, 2017). The maximum duration (360 hours, 15 days) was informed by a retrospective analysis of the nationwide inpatient sample from 1998-2000 that included 18,444 patients who underwent either open colectomy or laparoscopic colectomy for complications of diverticulitis (Guller et al, 2003). Data informing the RTDC probability come from studies regarding failure rates of initial conservative management (antibiotics +/- percutaneous drainage) for complicated diverticulitis. The minimum probability is based on a retrospective cohort of patients drawn from two databases in the UK, the Clinical Practice Research Datalink and the Hospital Episode Statistics. Patients with an incident case of perforated diverticulitis were included. 880 patients were managed without surgical intervention. 767/880 survived to discharge. 5.1% of survivors ultimately required surgical intervention. (Adiamah et al, 2021) In a similar retrospective cohort study of 135 patients with diverticular abscess in Canada managed with antibiotics and percutaneous drainage, 12.3% ultimately had surgery (Garfinkle et al, 2016). The maximum probability of RTDC is based on a single center randomized controlled trial of 137 patients with acute diverticulitis complicated by abscess at Westchester Medical Center, New York Medical College. Of the 81 patients assigned to antibiotics and percutaneous drainage, 15 (18.5%) failed conservative management, and required surgical intervention. The CRT capabilities for this scenario include antibiotics and percutaneous drainage. Thus, the RTDC probability was assigned a range of 5.1-18.5%. The minimum probability of LOCL for this scenario was assigned as 3.5% based on a 3.5% 30-day mortality rate in patients who received percutaneous drainage but not surgery for diverticular abscess (Gregersen et al, 2005). Chapman et al, 2005 reported an overall mortality for patients hospitalized with acute complicated diverticulitis of 6.5%. Adiamah et al, 2021 reported a survival rate of 96.3% at one year in patients under 65 years old (overall survival rate was much lower due to a dismal survival rate of only 39% in patients over 75 years). Given that the astronaut cohort is primarily under 65 years old, this corresponds to an LOCL probability of 4.7%. (Adiamah et al, 2021) The maximum probability 10.1% LOCL was also based on Gregersen et al, 2005, reported as the 30-day mortality rate for patients who received only antibiotics for diverticular abscess. Thus, the LOCL was assigned as 3.5-10.1%.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

There is a paucity of data regarding truly untreated acute uncomplicated diverticulitis. However, there are many studies comparing use of antibiotics vs. no antibiotics in the treatment of acute uncomplicated diverticulitis. For the purposes of estimating the duration for this scenario these studies will be utilized, in particular, the arm without antibiotic treatment. Jaung et al, 2021, in a double-blinded randomized controlled trial of 180 patients hospitalized across 4 hospitals in New Zealand and Australia with CT proven acute diverticulitis, reported that patients had an average of 3 days of symptoms prior to admission. Therefore, the minimum duration will be assigned 72 hours.

The duration of hospital stay in this study ranged from 26-60 hours. Chabok et al, 2012 reported a much longer duration of stay, in a similar multi-center randomized controlled trial of antibiotics vs. no antibiotics for acute uncomplicated diverticulitis involving 10 hospitals in Sweden and 1 hospital in Iceland, of 0-25 days in the untreated arm. In another randomized controlled trial of 528 patient with CT-proven acute primary, left-sided uncomplicated diverticulitis randomly assigned to observation vs. antibiotic treatment the inter-quartile range of 5-35 days (full range not provided) (Daniels et al, 2016). Therefore, the duration range for this scenario was assigned a range of 72-840 hours (3-35 days). Notably, these studies are based on hospitalized patients. The duration for acute uncomplicated diverticulitis that receives outpatient management is not captured by these data. The RTDC surrogate for this scenario is admission to the hospital. Bolkenstein et al, 2018 presented data based on a retrospective cohort study of 751 patients with uncomplicated diverticulitis. 264 patients were treated as outpatients, without antibiotics in this study. Of these, 12 (4.6%) experienced "treatment failure" defined as, "Admittance to the hospital, mortality, complications (perforation, abscess, colonic obstruction, urinary tract infection, pneumonia), need for antibiotics, operative intervention, or percutaneous abscess drainage within 30 days after initial presentation." Because this is based on outpatient care, 4.6% will be used as the minimum RTDC probability but may be an overestimate since it includes outcomes other than the need for hospitalization. Daniels et al, 2016, in a multi-center randomized controlled trial of CT-proven primary acute uncomplicated, left-sided diverticulitis in the Netherlands, reported a readmission rate of 17.6% in the arm that did not receive antibiotics. Jaung et al, 2021 reported a similar readmission rate of 11% at 30 days in the arm that did not receive antibiotics. Notably, Daniels et al, 2016 and Jaung et al, 2021 are studies of patients who were initially hospitalized and required re-admission. They may, therefore, be an overestimate of readmission rates. The RTDC probability was assigned a range of 4.6-17.6%. Jaung et al, 2021 reported no mortality in the untreated arm. Bolkenstein et al, 2018 reported no deaths directly related to an acute uncomplicated diverticulitis (3/0.53% deaths overall, but 1 was related to perforation and the other 2 were related to comorbidities of heart failure and myocardial infarction). Daniels et al, 2016 reported a mortality rate of 1.1% in the untreated arm. Therefore, the LOCL probability was assigned a range of 0-1.1%.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

There is a paucity of data regarding untreated complicated diverticulitis. The only available literature describes partial treatment and it was used to inform the duration for this scenario. In a retrospective cohort study of 3148 diverticulitis patients with a diverticular abscess, drawn from a database of all patients in Denmark between the years 2000-2012, patients were separated into arms by treatment; antibiotics only, percutaneous drainage, or surgery. The antibiotics only arm provided a range of hospital stay of 0-369 days (Gregersen et al, 2016). Interestingly, a similar study by Garfinkle et al, 2016 in Canada of 135 patients with diverticulitis and an abscess between 2000-2013 reports a much shorter length of stay of 6-12 days. The minimum duration for this scenario will be assigned 72 hours based on Jaung et al, 2021 stating the average duration of symptoms prior to presentation to the hospital with uncomplicated diverticulitis is 3 days because a similar statistic for complicated diverticulitis could not be found in the literature. The maximum duration will be assigned 369 days (Gregersen et al, 2016). Thus, the duration range was assigned 72-8856 hours. The RTDC surrogate for this scenario is the requirement for surgery. The RTDC probabilities for this scenario are based on the proportion of patients that underwent surgery from two cohort studies. The minimum probability of RTDC for this scenario was based on a retrospective cohort study of 685,390 patients drawn from the Nationwide Inpatient Sample databank. In 2005, 55% of cases of complicated diverticulitis were treated with colectomy (Ricciardi et al, 2009). The maximum probability of RTDC for this scenario was assigned as 98% based on the proportion of patients who underwent surgical intervention in a retrospective cohort of 337 complicated diverticulitis patients at the Mayo Clinic, Scottsdale between 1990-2003 (Chapman et al, 2005). Thus, the RTDC probability was assigned 55-98%. The minimum LOCL probability was assigned 26% based on the mortality rate reported in a retrospective cohort of 340 patients who required emergency surgery for perforated diverticulitis across five hospitals in Rotterdam, the Netherlands, between 1990 and 2005 (Vermeulen et al, 2009). Although this is not an untreated scenario, it was felt to be a reasonable surrogate for delayed presentation/intervention. The maximum probability was conservatively assigned 100% due to the paucity of data regarding untreated complicated diverticular disease.

TABLE 5. CLINICAL PHASE II DURATION LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 5 Caption.*
Shabanzadeh and Wille-Jørgensen, 2012	Terrestrial	3	The duration for the untreated best-case scenario was based on studies comparing antibiotics vs. no-antibiotics, specifically the "no-antibiotic" arm. The duration for the treated worst-case scenario are based on hospital-stay data for surgical interventions. The duration for the untreated worst-case scenario is based on complicated diverticulitis
Wilkins et al, 2013	Terrestrial		
Abraha et al, 2017	Terrestrial		

Jaung et al, 2021 Daniels et al, 2016 Chabok et al, 2012 Gregersen et al, 2016 Garfinkle et al, 2016 Guller et al, 2003	Terrestrial Terrestrial Terrestrial Terrestrial Terrestrial Terrestrial		patients who received antibiotics (instead of surgical intervention). The evidence informing the durations for this CLiFF includes review articles, Cochrane systemic reviews, cohort data, and RCT data. Most of the populations involved in these studies are foreign; Sweden, (Shabanzadeh and Wille-Jørgensen, 2012), Australia/New Zealand (Jaung et al, 2021), 3 European countries (Abraha et al, 2017), the Netherlands (Daniels et al, 2016), Sweden and Iceland (Chabok et al, 2012), Denmark (Gregersen et al, 2016), Canada (Garfinkle et al, 2016). Wilkins et al, 2013 is a review article from the American Academy of Family Physicians. Shabanzadeh and Wille-Jørgensen, 2012 and Abraha et al, 2017 are Cochrane reviews. RCT studies include: Jaung et al, 2021; Daniels et al, 2016; Chabok et al, 2012. Cohort studies include: Guller et al, 2003; Gregersen et al, 2016; and Garfinkle et al, 2016. Advanced age is a pre-disposing factor for diverticulitis. Three cohort studies had subjects that are older than the astronaut corps (median age 62-66yo; Abraha et al, 2017), (mean age 65.1yo; Gregersen et al, 2016), (mean age 61; Garfinkle et al, 2016). However, the RCT studies had subject with a mean age in their 50s (median 56-59yo; Jaung et al, 2021), median 56.3-57.4 yo; Daniels et al, 2016), (median 57.1-57.4; Chabok et al, 2012). The remaining cohort study (Guller et al, 2003) had a mean age of 59.8 yo. Because diverticulitis is more common in females, most studies had a female predominance (53-64%; Abraha et al, 2017), (50-53%, Jaung et al, 2021), (65%; Chabok et al, 2012), (57%; Gregersen et al, 2016), (54%; Guller et al, 2003). Two studies had a male predominance: (51% male; Daniels et al, 2016), (57.5% male, Garfinkle et al, 2016). Overall, given the quality of the evidence which includes 2 Cochrane Reviews and 3 RCTs, the level of confidence for the durations in this CLiFF was assigned a 3.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 6 Caption.*
Ricciardi et al, 2009 Chapman et al, 2005 Daniels et al, 2016 Jaung et al, 2021 Adiamah et al, 2021 You et al, 2018 Garfinkle et al, 2016 Etzioni et al, 2010 Bolkenstein et al, 2018	Terrestrial Terrestrial Terrestrial Terrestrial Terrestrial Terrestrial Terrestrial Terrestrial Terrestrial	3	RCTs comparing antibiotics vs. no-antibiotics were used to inform the untreated best-case scenario. Specifically, failure rates for the "no-antibiotic" arm were used to estimate the RTDC probability. The treated worst-case scenario RTDC was informed using data regarding failure rates for antibiotics +/- percutaneous drainage, but not surgery since surgical capabilities will require RTDC. There is a paucity of data regarding untreated complicated diverticulitis. The RTDC probability for the untreated, worst-case scenario is therefore based on the overall proportion of complicated diverticulitis patients in two cohort studies (Chapman et al, 2005; Ricciardi et al, 2009). The studies informing the RTDC probabilities include 3 RCTs and 6 cohorts. RCTs include: Jaung et al, 2021; Daniels et al, 2016; You et al, 2018. Cohort studies include: Chapman et al, 2005; Adiamah et al, 2021; Garfinkle et al, 2016; Etzioni et al, 2010; Bolkenstein et al, 2018; Ricciardi et al, 2009. Four studies had subjects that are older than the astronaut corps (67.4% of the study population aged 65+ yo; Adiamah et al, 2021), (mean age 61; Garfinkle et al, 2016), (mean age 65yo; Chapman et al, 2005), (mean age 68.5yo; Ricciardi et al, 2009). The remaining 5 studies had patients with an

			age that is more representative of the astronaut corps (mean age 58.5yo; Etzioni et al, 2010), (mean age 53.5-55.2yo; You et al, 2018), (median age 56.3-57.4 yo; Daniels et al, 2016), (median age 56-59 yo; Jaung et al, 2021), (mean age 58yo; Bolkenstein et al, 2018). Three studies were predominantly male: (57.5% male; Garfinkle et al, 2016), (61% male, You et al, 2018) (51% male, Daniels et al, 2016). The remaining six studies were predominantly female ranging from 50-61.4%). Only two studies involved American subjects (Chapman et al, 2005 and Etzioni et al, 2010). However, Jaung et al, 2016 involved Australian and New Zealand subjects and Garfinkle et al , 2016 was a Canadian study.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 7 Caption.*
Chapman et al, 2005	Terrestrial	3	LOCL for the untreated best-case scenario is based on mortality rates the no-antibiotic arm of studies that compared antibiotic treatment to no-antibiotic treatment (Jaung et al, 2018; Bolkenstein et al, 2018). The LOCL for the treated worst-case scenario is based on mortality rates in patients who received percutaneous drainage +/- antibiotics but not surgery (Gregersen et al, 2005). Similar mortality rates were provided by other sources (Chapman et al, 2005; Adiamah et al, 2021). There is a paucity of data regarding untreated complicated diverticulitis. The untreated worst-case scenario LOCL is based on patients who presented with perforation and required emergent surgery (Vermeulen et al, 2009) and the maximum probability was conservatively assigned 100%. The only study for LOCL that was not also used to inform either the duration or RTDC probabilities is Vermeulen et al, 2009; a cohort study reporting on 340 patients in the Netherlands with median age of 66 yo, 56% female.
Jaung et al, 2021	Terrestrial		
Bolkenstein et al, 2018	Terrestrial		
Daniels et al, 2016	Terrestrial		
Adiamah et al, 2021	Terrestrial		
Gregersen et al, 2016	Terrestrial		
Vermeulen et al, 2009	Terrestrial		

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Overview

The definition of uncomplicated acute diverticulitis is often vague and poorly defined. Uncomplicated acute diverticulitis is defined as localized diverticular inflammation without abscess or perforation. A universally accepted classification divides intra-abdominal infections (IAIs) into complicated and uncomplicated. In uncomplicated IAIs, the infection only involves a single organ and does not extend to the peritoneum, while in complicated IAIs, the infectious process extends beyond the organ, causing either localized or diffuse peritonitis. Many authors have also separated diverticulitis into different severity levels. As one example, there are different severities if there is a pericolic abscess, pelvic abscess, generalized purulent peritonitis, or fecal peritonitis present (Hinchey 1978). Our best-case definition implies an uncomplicated case that resolves spontaneously or with antibiotics while our worst-case definition is characterized by a complicated course that may require procedural or surgical management.

CNES: None

Diagnostic Scope and Resourcing

Diagnosis always starts with a history and physical exam inclusive of an abdominal exam and pelvic exam, if female, given cant miss conditions in the differential diagnosis. Laméris et al. developed a clinical decision rule for diagnosis terrestrially, based on 3 criteria: (1) direct tenderness only in the left lower quadrant, (2) CRP > 50 mg/l, and (3) absence of vomiting and found that 97% (95% CI 83–99%) of patients with all three criteria had diverticulitis. Andeweg et. al. (2011) developed a very similar diagnostic algorithm that was 86% accurate. In addition to these combination exam/lab algorithms, abdominopelvic ultrasound is 90% sensitive (CI 76-98%) and 90% specific (CI 86-94%) compared to CT which was 95% sensitive and 96% specific. However, CT scan will not be available.

Clinical Phase 1 Duration and Rationale
This version of IMPACT presumes physician level knowledge, skill, and ability will be present on the mission. The CRT working group SME consensus duration is as follows:
CP1 BC (Treated or Untreated): 1.75
CP1 WC (Treated or Untreated): 1.75
The highest scope of practice required for diagnosis includes the interpretation of the ultrasounds which is SOP 5 (attending).

Treatment Scope and Resourcing
The utility of antibiotics in acute uncomplicated acute diverticulitis is controversial given that several studies have demonstrated that antimicrobial treatment does not lead to significant improvement with mild disease. Thus, for best case scenario, as indicated in the definition, it may resolve with expectant management or antibiotics can be considered. Other treatments for mild diverticulitis include oral pain medications, antiemetics, and hydration.

For the worst-case scenario, oral antibiotics will be the mainstay of treatment. If getting sicker on oral antibiotics, the condition would likely escalate to the need for IV antibiotics and enter the sepsis CLiFF. Other considerations during a worst-case scenario include IV hydration, IV antiemetics, and insertion of a percutaneous drain. Surgical management, including laparoscopic lavage, will not be possible.

Communications and Support Needs
Ground communication for confirmation of diagnosis with video or pictures may be considered for the worst-case scenario to help guide management and guide RTDC decisions as the diagnosis warrants surgical management.

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IMM CLifF RECONCILIATION COMMENTS

The best- and worst-case definitions have very minor changes from the IMM definitions. In IMM the best case-scenario was defined as an uncomplicated case of diverticulitis, that is self-limited or responds to available non-surgical treatment. The current best-case scenario definition specifies that “non-surgical treatment” refers to oral or IV antibiotics. The IMM worst-case scenario was defined as a complicated case of diverticulitis, which may require surgical intervention. The current definition provides examples of complicated diverticulitis (i.e., abscess, perforation, fistula, obstruction) and specifies the requirement for IV antibiotics and/or percutaneous or surgical intervention. The durations provided in this CLiFF differ from the IMM CLiFF based on the updated evidence. In particular, the durations of the worst-case scenarios are much longer than that provided by the IMM CLiFF which provided a maximum duration of 24 hours for both worst-case scenarios. The RTDC probabilities in this CLiFF are lower than their counterparts in the IMM CLiFF. This is felt to be secondary to updated evidence that antibiotics are not necessary for many

uncomplicated cases of diverticulitis and advanced capabilities inflight including IV antibiotics and percutaneous drainage as detailed by the CRT. The LOCL values are similar between the CLiFFs. Variations in this CLiFF are due to updated evidence.

TABLE 8. TASK IMPAIRMENT CALCULATION BASED ON AFFECTED HUMAN SYSTEMS TASK CATEGORIES (HSTC)

	Clinical Phase 2: Treatment												
	Affected HSTCs												
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU	Hand (Dom)	Hand (Any)	Upper Extremity
Treated Best Case (TBC)		664					145				132		
Untreated Best Case (UTBC)		664		89			145				132		
Treated Worst Case (TWC)	223	664	113	89	854	44	145	5	13	6	132	564	414
Untreated Worst Case (UTWC)	223	664	113	89	854	44	145	5	13	6	132	564	414

	Affected HSTCs (Continued)					**Task Impairment Calculation**			**CP2 TI**
	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)					211	1152	3763	0.306138719	30.61387191
Untreated Best Case (UTBC)				34	211	1275	3763	0.338825405	33.88254053
Treated Worst Case (TWC)	22	196	34	34	211	3763	3763	1	100
Untreated Worst Case (UTWC)	22	196	34	34	211	3763	3763	1	100

	Clinical Phase 3: Condition End State												
	Affected HSTCs												
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU	Hand (Dom)	Hand (Any)	Upper Extremity
Treated Best Case (TBC)													
Untreated Best Case (UTBC)													

Treated Worst Case (TWC)													
Untreated Worst Case (UTWC)	223	664	113	89	854	44	145	5	13	6	132	564	414

	Affected HSTCs (Continued)					**Task Impairment Calculation**			**CP3 TI**
	Lower Extremity	Ambul & Standing (g)	Translation and Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)						0	3763	0	0
Untreated Best Case (UTBC)						0	3763	0	0
Treated Worst Case (TWC)						0	3763	0	0
Untreated Worst Case (UTWC)	22	196	34	34	211	3763	3763	1	100

TABLE 8 KEY

Human System Task Category (HSTC) Definitions:
Cognitive-Simple: Tasks requiring simple cognitive involvement (low levels of attention, following simple checklists, and not requiring extensive decision making) in conjunction with inputs from other systems. Cognitive-Complex: Tasks requiring complex cognitive involvement (requiring constant attention, frequent interpretation of outside stimuli to inform real-time situations) in conjunction with inputs from other systems.
Communication: Tasks requiring primarily communication, via hearing and speaking.
Interpersonal Skills: Tasks requiring interpersonal, social interaction between crew including complex technical tasks that require extended crew interaction.
Vision: Tasks in which visual information is required.
Hearing: Tasks in which primarily auditory information is required, excluding communication, e.g. hearing alarms, medical auscultation, OOHAs.
Cardiopulmonary: Tasks requiring greater-than-baseline cardiopulmonary effort, e.g. physically strenuous activities.
Dentition: Tasks requiring use of teeth for mastication.
GI (Gastrointestinal): Tasks requiring use of the alimentary system, e.g. solids/liquids consumption and solids excretion.
GU (Genitourinary): Tasks requiring use of the male/female genitourinary systems.
Hand (Dominant): Tasks performed using primarily the hand, requiring use of the dominant hand (piloting, medical procedures, dental procedures).
Hand (Any): Tasks performed using primarily the hand(s), with no preference for dominance, with equivalent bilateral effectiveness.
Upper Extremity: Tasks requiring specific use of the upper extremities, excluding hands.
Lower Extremity: Tasks requiring specific use of the lower extremities (excluding ambulation and standing in the presence of gravity), e.g. using exercise equipment.
Ambulation and Standing (g): Tasks requiring use of both lower extremities to accomplish ambulation or standing in the presence of gravity.
Translation and Stabilization (microgravity): Tasks requiring use of either the upper or lower extremities to accomplish translational movement and stabilization (securing oneself to remain stationary) in the setting of microgravity.
Don/Doff Equipment: Tasks requiring the donning of personal equipment (including pressure suit, exercise harness, EVA equipment, etc.).
Pressure Ops: EVA/contingency tasks performed while pressurized in a suit.

Criteria for Assignment of Conditions to HSTCs (any of the following)
1) Is affected crew member physically incapable of performing the human system task category, without impairment, with the condition?
2) Would the treatment (e.g., medications) impair the crewmember's ability to perform the human system task category? (Does not apply to UTx)
3) Does the condition have a high likelihood of causing a significant aeromedical contraindication with an associated human system task category
4) Would performing tasks in an associated task category worsen the condition? (If so, it is affected).
5) Does pain associated with the condition impair any further human system categories?

TASK IMPAIRMENT COMMENTS

CP2: No comment.
CP3: No comment.

EVIDENCE COLLECTION PROCESS

Mesh terms that most closely resembled the best-case and worst-case scenarios, and associated Conditions Included but Not Explicitly Stated (CNES), were utilized to build incidence, duration, RTDC, and LOCL searches by best- and worst-case.

Incidence:
Databases searched for spaceflight and analog incidence data included: PubMed®, Google Scholar™, NASA Technical Reports Server (NTRS) public search, Defense Technical Information Center (DTIC), and Barratt MR, Baker E, Pool SL. Principles of Clinical Medicine for Space Flight. New York, NY: Springer; 2019. 2nd Edition.
Databases searched for terrestrial incidence included: DynaMed®, PubMed®, and Google Scholar™.

Duration, RTDC, LOCL:
Databases searched for duration, RTDC, and LOCL included: DynaMed®, Cochrane, PubMed®, and Google Scholar™. Note, that if duration, RTDC, or LOCL data was found in a DynaMed® search, the other search engines were not included.

Relevant articles were selected and reviewed. If applicable, the article was included in the CLiFF.

LEVEL OF CONFIDENCE (LOC) SCORING

Articles obtained to update the evidence behind this CLiFF were scored by ExMC editors, based on their applicability to the Exploration Spaceflight environment using the following grading scale:
4 – Confident
3 – Somewhat confident
2 – Neutral
1 – Somewhat unconfident
0 – Not confident

The following considerations factor into the grading scale above:
- How closely does the paper describe the medical condition as defined by the IMPACT 1.0 Condition List (relevance)?
- How closely does the population included resemble the astronaut population?
- Quality of the paper (number of subjects, methods, etc.)
- How much does the editor trust the source of the evidence?

- How closely does the editor think that the data represents the exploration spaceflight environment?
- Other considerations, at the discretion of the editor, supported in the comments for LOE scoring.

CLiFF LIMITATIONS SUMMARY

• The incidence for this CLiFF is based on terrestrial data from Bharucha et al, 2015. These data came from the Rochester Epidemiology Project database. Known risk factors for diverticulitis include sedentary lifestyle, obesity, smoking, and overuse of NSAIDs. These pre-disposing factors are less common in the astronaut cohort than the general public, so the incidence is likely an overestimation of acute diverticulitis in the astronaut cohort. Further, the data in Bharucha et al, 2015 included recurrent cases of diverticulitis. It is assumed that once an astronaut had a case of diverticulitis, they would either have definitive care via surgery or be disqualified from spaceflight.
• This is not a limitation of this CLiFF but listed here to be carried forward for future iterations of the CLiFF. Bharucha et al, 2015 (terrestrial source informing incidence) provides valuable information on repeat diverticulitis infections. Future iterations of IMPACT hope to use this information.
• For the untreated best-case scenario, all studies used except Bolkentstein et al, 2018 are based on initially hospitalized patients and may therefore not reflect the true duration, RTDC, or LOCL for acute uncomplicated diverticulitis since they do not include data from patients treated as outpatients.
• There is a paucity of data regarding an untreated worst-case diverticulitis. The untreated worst-case scenario duration is based on diverticular disease with an associated abscess treated with antibiotics only. The RTDC is based on the proportion of complicated diverticulitis patients who required surgery in the listed studies. The LOCL is based on a study of patients presenting with perforation requiring emergent surgery (delayed/advanced presentation) and the upper limit of 100% was conservatively assigned since data does not exist to inform this value.

CLiFF ACRONYMS

ACRONYM	PHRASE	DEFINITION (IF APPLICABLE)
AAOMS	American Association of Oral and Maxillofacial Surgeons	
AMA	American Medical Association	
ARCL	All Remaining Conditions List	
ARS	Acute Radiation Sickness	
BHP	Behavioral Health and Performance	
CAC	Coronary Artery Calcium	
CHS	Crew Health and Safety	
CL	Condition List	
CLiFF	Clinical Finding Form	
CMO	Crew Medical Officer	
COMFORT	Clinical Outcome Metrics for Optimization of Robust Training	
CP1	Clinical Phase 1	
CP2	Clinical Phase 2	
CP3	Clinical Phase 3	
CRL	Clinical Resource Level	
CRT	Capability Resource Table	
CST	Clinical Science Team	
CT	Computed Tomography	
DCS	Decompression Syndrome	
DRM	Design Reference Mission	
ED	Emergency Medicine Doctor	

EL	Evidence Library
EMCL	Exploration Medical Condition List
EMT	Emergency Medical Technician
EVA	Extravehicular Activity
EXMC	Exploration Medical Capability
HRP	Human Research Program
ICD	International Classification of Disease
ICL 1.0	IMPACT 1.0 Medical Conditions List
ICU	Intensive Care Unit
IMCL	imbed Condition List
imbed	Integrated Medical Evidence Database
IMM	Integrated Medical Model
IMPACT-MD	Impact Medical Database
IP	Incidence Proportion
IR	Incidence Rate
ISS	International Space Station
IV	Intravenous
JSC	Johnson Space Center
LEO	Low-Earth orbit
LEVA	Lunar Extravehicular Activity
LOCL	Loss of Crew Life
LOM	Loss of Mission
LSAH	Lifetime Surveillance of Astronaut Health
LSO	Lunar Surface Operations
MCL	Master Condition List
MEVA	Medical Extravehicular Activity
NASA	National Aeronautics and Space Administration
N/A	Not Applicable
NP	Nurse Practitioner
OBGYN	Obstetrics and Gynecology
OR	Occurrence Rate
PA	Physician Assistant
PDQ	Pain Disability Questionnaire
PFCL	Proposed Future Conditions List
PPE	Personal Protective Equipment
PTRS	Project Technical Requirements Specification
PRL	Pharmaceutical Resource Level
QTL	Quality Time Lost

RCL	Removed Conditions List	
RCT	Randomized Controlled Trial	
REP	Rochester Epidemiology Study	
RTDC	Removal to Definitive Care	
SANS	Spaceflight-Associated Neuro-ocular Syndrome	
SAS	Space Adaptation Syndrome	
SEVA	Spaceflight Extravehicular Activity	
SME	Subject Matter Expert	
SoP	Standard Operating Procedure	
SPE	Solar Particle Event	
TI	Task Impairment	

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ICL97 Space Adaptation - Space Motion Sickness Clinical Findings Form (CLiFF)

OVERVIEW

Space Motion Sickness (SMS) is a phenomenon that is experienced by large proportion of spaceflight crew members, up to 60% (Davis et al., 1998; Ortega et al., 2019), that results in general malaise, nausea, gastrointestinal discomfort, and fatigue. There are several theories to explain its etiology including cephalad fluid shifts and neuroanatomical sensory conflicts (Russomano et al., 2019; Lackner et al., 2006). SMS is considered to be part of Space Adaptation Syndrome. This CLiFF condition only includes SMS which initiates from transitioning from gravity to microgravity. Entry Motion Sickness (EMS) or Earth-readaptation syndrome is a similar condition that results from transitioning from microgravity to gravity, and is handled in a different CLiFF.

INCIDENCE DATA INCLUDED IN MODEL

The model imports the following incidence information from the MEDPRAT Evidence Library Database: incidence data category, space adaption status, EVA status, incidence data type, incidence and occurrence distribution data and incidence data characteristics. *Data category* defines the type of data available for incidence calculations (i.e., raw data vs. adjusted data). *Space adaptation* identifies medical events that where onset occurs in the first 5-7 days of flight and does not reoccur. EVA-related incidence values identify medical events that occur only during an EVA. Incidence values types vary by data category and define the number of medical events per person-year (rates) or medical events per person at-risk (proportion) for each medical condition. Incidence values can be modified by crew characteristics such as gender sex and certain crew medical history characteristics. Modifying characteristics are noted below and incidence values are listed individually for each characteristic. Distributions are assigned to medical events incidence values and occurrences in the model. For each crewmember in a given trial, the incidence and number of occurrences of each medical condition are randomly selected from these probability distributions. Detailed descriptions of the distributions are included in the MEDPRAT Technical Description Document.

INCIDENCE DATA

SPACEFLIGHT LITERATURE

This condition is tied explicitly to being in spaceflight, and consequently incidence from LSAH pulls and previous IMM efforts are rated most highly. Unfortunately, at the time of this CLiFF completion, a repeat LSAH gathering event was not possible and missions past 2017 are not represented. Of note, ***the authors of this CLiFF recommend that should a repeat LSAH pull become available, the incidence for this CLiFF condition be recalculated given the many limitations and assumptions needed to interpret the prior IMM incidence calculation.***

In the prior CLiFF effort, entitled “Space Motion Sickness (space adaptation)”, the authors did not use LSAH data from the Walton pull as they believed that this condition was significantly under-reported in the early missions. Instead, data gathered from the Ortega et al. (2008) for Barratt et al (2008) which stemmed from Reschke et al. (1993 and 1996). The crewmembers from Mercury and Gemini (a total of n=26) were subtracted as the other conditions in IMM did not account for these missions. The authors report: “the incidences per mission are: Apollo 11/33 = 0.33; Skylab 5/9 = 0.56; Apollo-Soyuz Test Project = 0; Space Shuttle, 1981-1986 57/85= 0 .67,

1988-1998, 252/315 = 0.80." which led to "the cumulative incidence (# events / # crew) for the US space program, from 1962 to 1998 is (325/445) = 0.73." When reviewing this data in the recent corresponding Barratt chapter (2019), the authors of this effort noted some inconsistencies. For example, Shuttle 81-86 is reported as 74 events/103 mission. Further, the Ortega et al. (2019) hypothesize in their chapter that events were less frequent in the early missions as crewmembers had less freedom of movement in their smaller cabin sizes, which is a protective factor against space motion sickness. The previous CLiFF furthers adds data from the Saile pull (2017): "Added the incidence information from the real world system. Added 95 new medical events (18 ISS for a total of 18 and 77 STS to the existing 309 events for total of 386 STS events). Added 144 persons at risk to the 445 persons at risk for a new total of 589 persons at risk (Saile, 2017). Updated the Persons at Risk based on the revised real world system integrated incidence data. The integrated RWS persons at risk from 144 to 143 so the conditions integrated iMED value went from 589 to 588 (Saile L., 2017)." Incidence calculated for the prior CLiFF was noted to be 419 events/588 persons at risk. Again, the authors of this effort do not have access to the raw LSAH data, but they are unable to reconcile why the number of events was not 420 (=325 + 95). After consultation with the biostatistician, the authors of this effort chose to not change the previous IMM incidence uncorrected as there was no way to determine which calculations were more right than others without the raw data. However, should future LSAH pulls occur, it is recommended that a new incidence be recalculated using updated data, including the early missions.

Antonsen et al. (2017) was rated less highly than the data in the previous IMM CLiFF as the data compiled in these tables come directly from LSAH pulls as well and Table 1 could not be adequately reconciled with this specific condition's definition. For example, 'SMS', 'Vestibular' and 'Fluid Shift categories are all potentially related to this condition." Table 1 was mislabeled as 'ISS through Exp 40' when it should read ' ISS expeditions 9 and 14 through 40'. Of note, there are 325 events (similar to what is reported in the previous IMM effort above) in Table 2. The authors of this CLiFF wonder whether, the authors of the previous effort had mistakenly used this value rather than individually adding the incidences per mission as they report.

There are several other individual studies detailing both the United States and Russian (or Soviet Union) experience with SMS (Davis et al., 1988; Heer et al., 2006, Oman et al., 1996, Gontcharov et al., 2005) however these studies were downrated secondary to limited years of inclusivity and often small sample sizes.

ANALOG LITERATURE

SMS has been attempted to be replicated by the similar conditions that evokes space adaptation-headache (ICL 94) with a head-down tilt bed rest (Prakash et al., 2015). However, unlike in space adaptation-headache, this is not a clinically relevant method for inducing SMS.

TERRESTRIAL LITERATURE

This is a space-related condition and there are no applicable terrestrial studies.

TABLE 1. OVERALL INCIDENCE SUMMARY

Incidence	mean 0.7121 person-missions and SD 0.01875	*Table 1 Caption.* The Bayesian posterior distribution for the incidence proportion given the spaceflight data (419 events over 588 person-missions) under an uninformative prior is Beta(shape1=414.55, shape2=167.6) with mean 0.7121 person-missions and SD 0.01875. Spaceflight evidence – 419 events over 588 person-missions. IP: 0.7126 (95%CI: 0.6742, 0.7489) This translates to a Beta (shape1=414.55, shape2=167.6) distribution.

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	*Source*	*LOC Value*	*Table 2 Caption.*
Ortega et al., 2008	Spaceflight	3	Spaceflight incidence data was rated the highest as this is a condition, by definition, that can only occur in space. Analog and terrestrial studies would not accurately represent incidence for this condition.
Reshcke et al., 1993	Spaceflight	1	
Reshcke et al., 1993	Spaceflight	1	
Ortega et al., 2019	Spaceflight	3	
Saile et al., 2017	Spaceflight	3	
Antonsen et al., 2017	Spaceflight	2	
Davis et al., 1988	Spaceflight	1	
Heer et al., 2006	Spaceflight	1	
Oman et al., 1996	Spaceflight	1	
Gontcharov et al., 2005	Spaceflight	1	
Prakash et al., 2015	Analog	0	

CREWMEMBER SELECTION/PREVENTION

DISQUALIFYING CONDITIONS

Refer to Medical Evaluation Documents (MED) Volume A, Medical Standards for ISS Crewmembers, International Space Station Program, Rev 3.4 (2016).

PREFLIGHT PREVENTIVE MEASURES

This CLiFF condition is event-based and consequently there are no known preventative measures. However, to help exclude other causes of neurological pathologies, at L-21/18 months, if greater than 2 years since ISS section, crewmembers undergo MRI/MRA neuroimaging, a full annual medical exam L-6/9 months and brief medical exams at L-7/10 and L-1/2 days by the Flight Surgeon.

BEST CASE SCENARIO DEFINITION

Space motion sickness including mild to moderate symptoms (e.g. loss of appetite, malaise, stomach awareness, 2 or fewer episodes of emesis, resolves within 72 hours, causes no or minimal performance decrement).

WORST CASE SCENARIO DEFINITION

SMS with severe and persistent symptoms (e.g. need to keep head from moving, greater than 2 episodes of emesis, significant performance decrement, persists for greater than 72 hours).

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

Per the prior IMM iteration: "The BC/WC percentages were updated based on the empirical data from the Real World System data set. We are estimating our worst-case scenario at 3.19% (3/94), thus our best case is 96.81% 91/94 (Saile L., 2017)." However, in Davis et al. (1988) and replicated in Barratt et al. (2019), severe cases were defined almost exactly to the worst-case definition ("…more than two episodes of vomiting...") and accounted for 15% of all SMS cases., whereas mild cases were 49% and moderate cases were 36%. The reason for the discrepancy between these two sources is currently unclear, but the authors of this CLiFF chose to use the more recent reported LSAH calculations given that it is inclusive of the later missions. **However, should a LSAH pull occur in the next effort, the authors recommend repeating this calculation and justifying the discrepancy.**

TABLE 3. BEST/WORST CASE PROBABILITY LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 3 Caption.*
Saile et al., 2017 Davis et al., 1988	Spaceflight Spaceflight	3 2	Only spaceflight data was utilized given the condition's definition. Worst-case probability estimates from the previous IMM CLiFF effort were used as there had been no further studies published in the interim.

TABLE 4. CLiFF TREATMENT & OUTCOME TABLE BY CLINICAL PHASE

Case Scenario	***Incidence****	***Condition Probability^***	***CP1: Diagnosis***		***CP2: Treatment***			***CP3: Condition End State***				
			TI%	***Duration***	***TI%***	***Duration***		***TI%***	***RTDC***		***LOCL***	
			Preset	Preset	Preset	Min	Max	Preset	Min %	Max %	Min %	Max %
Treated Best Case (TBC)	mean: 0.7121 person-missions SD: 0.01875	97	100%	0.53	13.314	0	72	0	0	0	0	0
Treated Worst Case (TWC)		3	100%	0.53	30.959	72	336	0	0	0	0	0

Untreated Best Case (UTBC)	*N/A*	*N/A*	*N/A*	0.53	33.324	0	72	0	0	0	0	0
Untreated Worst Case (UTWC)	*N/A*	*N/A*	*N/A*	0.53	66.729	72	336	0	0	0	0	0

TABLE 4 KEY

Incidence: The same incidence will be used for both TBC and TWC. For EVA conditions: events per EVA (events/EVA). For space adaptation conditions: events per person (events/person). For non-spaceflight conditions: events per person year (events/py).

^Condition Probability: The probability that CliFF condition progresses to a worst case scenario. Best case scenario: 100%-Worst Case.

Clinical Phase General Comments:

- TI% = Task Impairment %. Task Impairment is the % of tasks that the crewmember is incapable of performing without impairment secondary to the medical condition.
- Durations are defined in hours.
- Removal to Definitive Care (RTDC): The probability the entire crew aborts the mission and returns to earth. This is considered as a condition end state result if any of the following criteria are met: 1) the potential for LOCL, 2) potential for significant permanent task impairment, or 3) potential for intractable pain.
- Loss of Crew Life (LOCL): The probability of death of affected crewmember due to medical condition.

Clinical Phase 1: Initial Assessment and Diagnosis

- Covers only the initial assessment and diagnosis of the affected crewmember to define his or her medical condition. While the affected crewmember is being assessed, he or she is not able to perform any assigned tasks, thus Task Impairment (TI) during this phase is considered 100%. In the untreated case, there is no diagnosis performed, therefore Task Impairment and Duration will always be “not applicable."

Clinical Phase 2: Stabilization, Treatment, and Convalescence

- The affected crewmember is receiving any appropriate initial or follow-on treatment for his or her medical condition to allow the crewmember to recover as much as he or she is able to recover in the spaceflight environment. Clinical phase 2 also encompasses relapses or recurrences of the same original medical condition in Clinical Phase 1. The duration of Clinical Phase 2 is expressed as minimum and maximum hours.

Clinical Phase 3: Condition End State

- Reached once the affected crewmember has recovered from the medical condition as much as he or she is able to recover in the spaceflight environment amongst treated and untreated best and worst case scenarios. This may or may not be recovery from the given medical condition to the full extent possible. If this “recovered” state results in Removal to Definitive Care (RTDC) or Loss of Crew Life (LOCL) this will be noted in the condition end state results.

SCENARIO OVERVIEW COMMENTS

Space motion sickness is part of space adaptation syndrome and is thought as a response of the neuro-vestibular system adapting to microgravity (Ortega et al., 2019). Symptoms of this condition have included nausea, pallor, cold sweating, increased salivation, drowsiness, pain, and central nervous system defects (Graybiel et al., 1968). Most symptoms develop within the first hours of microgravity but have begun to resolve or have dissipated completely by 72-96 hours (Lackner et al., 2006). The best-case adheres to this typical pattern and the worst-case refers to a particularly symptomatic case that continues persist past the fourth day. Given that this condition only exists in microgravity, there is no acceptable RTDC terrestrial-surrogate for this condition.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

Symptoms of SMS can occur within minutes of being in microgravity (Ortega et al., 2019); hence the lower bound for duration was set at zero hours. The treated worst-case is defined as having both severe and persistent symptoms, greater than 72 hours. Consequently, the upper bound of duration was set at 72 hours.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

By definition, the lower bound for the worst-case is set at 72 hours. In Matsnev et al. (1983) there was a case of SMS that continued over 14 days inflight, creating the upper bound. In the Russian long-duration mission experience, some astronauts intermittently experienced symptoms throughout their entire stay during microgravity (Ortega et al.2019; Kornilova et al., 1996). Still, these occurrences were described as relatively benign and did not affect mission tasks. To date, there have been no instances of RTDC or LOCL secondary to this condition in spaceflight.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

There exists little accessible data regarding duration for the untreated best case. Subject matter expert consensus was that it would be no less than the treated best-case-scenario. Again, RTDC and LOCL are not expected for this condition.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

Duration is expected to be no less than the treated worst-case-scenario. To date, there have been no instances of RTDC or LOCL secondary to this condition in spaceflight

TABLE 5. CLINICAL PHASE II DURATION LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 5 Caption.*
Ortega et al., 2019 Matsnev et al., 1983 Kornilova et al., 1996	Spaceflight Spaceflight Spaceflight	4	The duration of SMS has been well characterized in several reviews, cross-sectional surveys and case reports.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 6 Caption.*
Walton, 2010 Saile et al., 2017	Spaceflight Spaceflight	4	Only spaceflight data was utilized given the condition's definition.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	***Source***	***LOC Value***	*Table 7 Caption.*
Walton, 2010 Saile et al., 2017	Spaceflight Spaceflight	4	Only spaceflight data was utilized given the condition's definition.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope

Overview

Space adaptation motion sickness is a common condition experienced by most astronauts. It can often be exacerbated by frequent rapid head movements soon after entering microgravity, and mitigated by limiting such movements until the brain has had time to adapt to the new surroundings.

CNES: NONE

Diagnostic Scope and Resourcing
Diagnosis relies on history and physical exam

Clinical Phase 1 Duration and Rationale
This version of IMPACT presumes physician level knowledge, skill, and ability will be present on the mission. The CRT working group SME consensus duration is as follows:

CP1 BC (Treated or Untreated): 0.53 hours for set up, history, and physical exam.

CP1 WC (Treated or Untreated): 0.53 for a set up, history, and a more thorough exam including neurological, fundoscopic, and vision testing to rule out other, more dangerous causes of headaches.

This condition requires a Scope of Practice 4 to manage and rule out other similar presenting conditions, assess treatment response, and assess fitness for duty. However, most of the treatment will not rise above level 1 and the more common best case requires only SoP 1.

Treatment Scope and Resourcing
The best case is mild and treatment includes oral antiemetics. The worst case has the same treatment but lasts longer and will require additional doses of antiemetics. Ondansetron is given a primacy of 1. Anti-vertigo medications are also included for the worst case. and a reassessment of the patient.

Communications and Support Needs;

Communications are not expected to be necessary beyond the routine medical ground communications given the context and frequency of this condition. However, it is expected that routine ground communication will be present and available to assist with treatment.

References
Barratt, Michael R., Ellen S. Baker, and Sam L. Pool. 2019. "Principles of clinical medicine for space flight." In. New York, NY: New York, NY : Springer.

IMM CLiFF RECONCILIATION COMMENTS

The predecessor to this CLiFF was entitled “Space Motion Sickness (space adaptation).” Given lack of access to the original LSAH pulls and this being a condition that only occurs in microgravity, many of the resources between this CLiFF and the prior iteration remain the same. For this effort, with the help of a biostatistician, incidence data was updated to reflect person-missions rather than person-years as this condition can only be expected to occur at the initiation of spaceflight. The authors of this CLiFF did not agree with the duration values in the prior effort, and these were updated to better reflect the best- and worst-case definitions with a broader literature search.

TABLE 8. TASK IMPAIRMENT CALCULATION BASED ON AFFECTED HUMAN SYSTEMS TASK CATEGORIES (HSTC)

	Clinical Phase 2: Treatment												
	Affected HSTCs												
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU	Hand (Dom)	Hand (Any)	Upper Extremity
Treated Best Case (TBC)							145		13		132		
Untreated Best Case (UTBC)		664		89			145		13		132		
Treated Worst Case (TWC)		664					145		13		132		
Untreated Worst Case (UTWC)	223	664		89			145		13		132	564	414

	Affected HSTCs (Continued)					Task Impairment Calculation			CP2 TI
	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)					211	501	3763	0.133138453	13.31384534
Untreated Best Case (UTBC)					211	1254	3763	0.333244752	33.32447515
Treated Worst Case (TWC)					211	1165	3763	0.30959341	30.95934095
Untreated Worst Case (UTWC)	22		34		211	2511	3763	0.667286739	66.72867393

	Clinical Phase 3: Condition End State
	Affected HSTCs

	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU	Hand (Dom)	Hand (Any)	Upper Extremity
Treated Best Case (TBC)													
Untreated Best Case (UTBC)													
Treated Worst Case (TWC)													
Untreated Worst Case (UTWC)													

	Affected HSTCs (Continued)					**Task Impairment Calculation**			**CP3 TI**
	Lower Extremity	Ambul & Standing (g)	Translation and Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)						0	3763	0	0
Untreated Best Case (UTBC)						0	3763	0	0
Treated Worst Case (TWC)						0	3763	0	0
Untreated Worst Case (UTWC)						0	3763	0	0

TABLE 8 KEY

Human System Task Category (HSTC) Definitions:

Cognitive-Simple: Tasks requiring simple cognitive involvement (low levels of attention, following simple checklists, and not requiring extensive decision making) in conjunction with inputs from other systems. Cognitive-Complex: Tasks requiring complex cognitive involvement (requiring constant attention, frequent interpretation of outside stimuli to inform real-time situations) in conjunction with inputs from other systems.

Communication: Tasks requiring primarily communication, via hearing and speaking.

Interpersonal Skills: Tasks requiring interpersonal, social interaction between crew including complex technical tasks that require extended crew interaction.

Vision: Tasks in which visual information is required.

Hearing: Tasks in which primarily auditory information is required, excluding communication, e.g. hearing alarms, medical auscultation, OOHAs.

Cardiopulmonary: Tasks requiring greater-than-baseline cardiopulmonary effort, e.g. physically strenuous activities.

Dentition: Tasks requiring use of teeth for mastication.

GI (Gastrointestinal): Tasks requiring use of the alimentary system, e.g. solids/liquids consumption and solids excretion.

GU (Genitourinary): Tasks requiring use of the male/female genitourinary systems.

Hand (Dominant): Tasks performed using primarily the hand, requiring use of the dominant hand (piloting, medical procedures, dental procedures).

Hand (Any): Tasks performed using primarily the hand(s), with no preference for dominance, with equivalent bilateral effectiveness.

Upper Extremity: Tasks requiring specific use of the upper extremities, excluding hands.

Lower Extremity: Tasks requiring specific use of the lower extremities (excluding ambulation and standing in the presence of gravity), e.g. using exercise equipment.

Ambulation and Standing (g): Tasks requiring use of both lower extremities to accomplish ambulation or standing in the presence of gravity.

Translation and Stabilization (microgravity): Tasks requiring use of either the upper or lower extremities to accomplish translational movement and stabilization (securing oneself to remain stationary) in the setting of microgravity.

Don/Doff Equipment: Tasks requiring the donning of personal equipment (including pressure suit, exercise harness, EVA equipment, etc.).

Pressure Ops: EVA/contingency tasks performed while pressurized in a suit.

Criteria for Assignment of Conditions to HSTCs (any of the following)

1) Is affected crew member physically incapable of performing the human system task category, without impairment, with the condition?
2) Would the treatment (e.g. medications) impair the crewmember's ability to perform the human system task category? (Does not apply to UTx)
3) Does the condition have a high likelihood of causing a significant aeromedical contraindication with an associated human system task category
4) Would performing tasks in an associated task category worsen the condition? (If so, it is affected).
5) Does pain associated with the condition impair any further human system categories?

TASK IMPAIRMENT COMMENTS

CP2: No comment.

CP3: No comment.

EVIDENCE COLLECTION PROCESS

Mesh terms that most closely resembled the best-case and worst-case scenarios, and associated Conditions Included but Not Explicitly Stated (CNES), were utilized to build incidence, duration, RTDC, and LOCL searches by best- and worst-case.

Incidence:
Databases searched for spaceflight and analog incidence data included: PubMed, Google Scholar, NASA Technical Reports Server (NTRS) public search, Defense Technical Information Center (DTIC), and Barratt MR, Baker E, Pool SL. Principles of Clinical Medicine for Space Flight. New York, NY: Springer; 2019. 2nd Edition. Databases searched for terrestrial incidence included: DynaMed, PubMed, and Google Scholar.

Duration, RTDC, LOCL:
Databases searched for duration, RTDC, and LOCL included: Dynamed, Cochrane, PubMed, and Google Scholar. Note, that if duration, RTDC, or LOCL data was found in a DynaMed search, the other search engines were not included.

Relevant articles were selected and reviewed. If applicable, the article was included in the CLiFF.

LEVEL OF CONFIDENCE (LOC) SCORING
Articles obtained to update the evidence behind this CLiFF were scored by ExMC editors, based on their applicability to the Exploration Spaceflight environment using the following grading scale: 4 – Confident 3 – Somewhat confident 2 – Neutral 1 – Somewhat unconfident 0 – Not confident The following considerations factor into the grading scale above: • How closely does the paper describe the medical condition as defined by the IMPACT 1.0 Condition List (relevance)? • How closely does the population included resemble the astronaut population? • Quality of the paper (number of subjects, methods, etc.) • How much does the editor trust the source of the evidence? • How closely does the editor think that the data represents the exploration spaceflight environment? • Other considerations, at the discretion of the editor, supported in the comments for LOE scoring.

LIMITATIONS SUMMARY
• The incidence should be considered a floor as some crewmembers may have minimized or denied their symptoms over fear of not being considered for future crew assignment. This was probably more of an issue during the Shuttle era when spaceflight lasted 2 weeks or less than it is during long-duration flights. • The authors did not have access to the original LSAH data and thus there was an implied dependence on already published sources. In the prior IMM CLiFF, the Walton LSAH pull was not used, and the authors of this CLiFF were unable to reconcile their calculations. • There may be some overlap between this condition and other CLiFF conditions, such as space adaptation headache. • Several assumptions needed to be made regarding duration and the untreated cases given lack of available studies.

ACRONYMS

ACRONYM	PHRASE	DEFINITION (IF APPLICABLE)

AAOMS	American Association of Oral and Maxillofacial Surgeons
AMA	American Medical Association
ARCL	All Remaining Conditions List
ARS	Acute Radiation Sickness
BHP	Behavioral Health and Performance
CAC	Coronary Artery Calcium
CHS	Crew Health and Safety
CL	Condition List
CLiFF	Clinical Finding Form
CMO	Crew Medical Officer
COMFORT	Clinical Outcome Metrics for Optimization of Robust Training
CP1	Clinical Phase 1
CP2	Clinical Phase 2
CP3	Clinical Phase 3
CRL	Clinical Resource Level
CRT	Capability Resource Table
CST	Clinical Science Team
DCS	Decompression Syndrome
DRM	Design Reference Mission
ED	Emergency Medicine Doctor
EL	Evidence Library
EMCL	Exploration Medical Condition List
EMT	Emergency Medical Technician
EVA	Extravehicular Activity
EXMC	Exploration Medical Capability
HRP	Human Research Program
ICD	International Classification of Disease
ICL 1.0	IMPACT 1.0 Medical Conditions List
ICU	Intensive Care Unit
IMCL	iMED Condition List

iMED	Integrated Medical Evidence Database
IMM	Integrated Medical Model
IMPACT-MD	Impact Medical Database
IP	Incidence Proportion
IR	Incidence Rate
ISS	International Space Station
IV	Intravenous
JSC	Johnson Space Center
LEO	Low-Earth orbit
LEVA	Lunar Extravehicular Activity
LOCL	Loss of Crew Life
LOM	Loss of Mission
LSAH	Lifetime Surveillance of Astronaut Health
LSO	Lunar Surface Operations
MCL	Master Condition List
MEVA	Medical Extravehicular Activity
NASA	National Aeronautics and Space Administration
N/A	Not Applicable
NP	Nurse Practitioner
OBGYN	Obstetrics and Gynecology
OR	Occurrence Rate
PA	Physician Assistant
PDQ	Pain Disability Questionnaire
PFCL	Proposed Future Conditions List
PPE	Personal Protective Equipment
PTRS	Project Technical Requirements Specification
PRL	Pharmaceutical Resource Level
QTL	Quality Time Lost
RCL	Removed Conditions List
REP	Rochester Epidemiology Study
RTDC	Removal to Definitive Care

SANS	Spaceflight-Associated Neuro-ocular Syndrome	
SAS	Space Adaptation Syndrome	
SEVA	Spaceflight Extravehicular Activity	
SME	Subject Matter Expert	
SoP	Standard Operating Procedure	
SPE	Solar Particle Event	
TBD	To Be Determined	
TI	Task Impairment	

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APPENDIX C IMPACT 1.0 CONDITION LIST (ICL 1.0)

TABLE C-1 ICL 1.0, v1 (initial) to v3.2 (final) with Definition Changes

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL1	ABDOMINAL WALL HERNIA	Asymptomatic or mildly symptomatic hernia not requiring surgery.	Hernia requiring either non-emergent surgery or emergent surgery due to complications.			
ICL2	ABNORMAL UTERINE BLEEDING	Irregular bleeding between menses, menses > 8 days in length, or heavy menses (requiring tampon/pad changes < Q2H, or passing clots larger than the size of a quarter), that resolves spontaneously or with medications.	Irregular bleeding between menses, menses > 8 days in length, or heavy menses (requiring tampon/pad changes < Q2H, or passing clots larger than the size of a quarter), that requires mechanical/surgical intervention.	Menses, Irregular Menorrhagia	-	
ICL3	ACUTE CORONARY SYNDROME	Unstable angina (unable to exercise without symptoms), or myocardial infarction that can be treated successfully with medications, without clinical signs of congestive heart failure (CHF).	Myocardial infarction resulting in a crewmember suffering-signs of symptomatic CHF. (Note cardiogenic shock is a separate condition).	Myocardial Infarction Angina, Unstable		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL4	ACUTE RADIATION SYNDROME	A single exposure dose exceeding the NASA 30d exposure limit of 250mGy (but less than 500mGy) to blood forming organs.	A single exposure dose exceeding 500mGy to blood forming organs.	A single exposure dose less than 1.2 Gy to blood forming organs, resulting in nausea and fatigue that impact mission objectives, but resolve spontaneously or with antiemetics within 4 days.		
ICL5	ALLERGIC REACTION (MILD TO MODERATE)	A crewmember with an allergic reaction that is quickly relieved by topical medications or one dose of oral medication.	A crewmember with a more severe allergic reaction; able to be treated with multiple doses of oral medication.		A crewmember with an allergic reaction that is quickly relieved by one dose of oral medication.	A crewmember with a more severe allergic reaction; able to be treated with oral medication but requires multiple doses and a longer duration of treatment.
ICL6	ALTITUDE SICKNESS	High altitude headache or acute mountain sickness (AMS); which resolves spontaneously, or with oxygen use, medications, or descent.	High altitude pulmonary edema (HAPE) or high-altitude cerebral edema (HACE).	High Altitude Headache High Altitude Pulmonary Edema High Altitude Cerebral Edema	High altitude headache or acute mountain sickness (AMS); which resolves spontaneously, with normalization of oxygen partial pressures, medications, or descent.	High altitude pulmonary edema (HAPE) or high-altitude cerebral edema (HACE).
ICL7	ANAPHYLAXIS	An anaphylactic event that responds to initial treatment with 1-2 doses of epinephrine.	An anaphylactic shock requiring supportive care.	Shock - Anaphylactic	An anaphylactic event that responds to initial treatment.	An anaphylactic event that responds to initial treatment.
ICL8	APPENDICITIS	Appendicitis which responds to conservative medical treatment (antibiotics and symptomatic treatment).-	Appendicitis resulting in a perforation or intra-abdominal infection.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL9	ARTHRITIS, ACUTE	Acute osteoarthritis flare or crystalline arthropathy with mild to moderate symptoms that responds to treatment. (Note rheumatologic arthropathies are not covered in this condition).	Acute osteoarthritis flare or crystalline arthropathy with severe symptoms requiring more than one course of treatment. (Note rheumatologic arthropathies are not covered in this condition).	Osteoarthritis, acute Arthropathy, acute - crystalline		
ICL10	ATRIAL FIBRILLATION/ ATRIAL FLUTTER	Atrial fibrillation or flutter that does not require emergent cardioversion, rate/rhythm control, or thromboembolic prophylaxis.	Atrial fibrillation or flutter that requires emergent cardioversion, rate/rhythm control, or thromboembolic prophylaxis.			
ICL11	BAROTRAUMA (EAR/SINUS BLOCK)	Mild barotrauma including minimal ear or sinus pain and/or fullness that responds to analgesics and decongestants.	Moderate to severe barotrauma, including symptoms of significant ear and/or sinus pain, hearing loss, vertigo, nausea, dizziness, and/or ear canal hemorrhage or epistaxis that may require surgical repair (e.g., oval window rupture).	Oval Window Rupture		
ICL12	BENZODIAZAPINE OR OPIOID OVERDOSE	A benzodiazepine or opioid medication overdose that resolves within 8 hours and does not require treatment.	A benzodiazepine or opioid medication overdose that requires more than 8 hours to resolve and/or requires treatment.		A benzodiazepine or opioid medication overdose that results in a respiratory perturbation but oxygen saturation that remains above 88%.	A benzodiazepine or opioid medication overdose that results in a respiratory perturbation causing an oxygen saturation to decrease below 88%.

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL13	BHP - ADJUSTMENT DISORDER	Adjustment reactions caused by stressful events that alleviate without any impact to the mission or personal life, and/or requires pharmacological therapy PRN, or behavioral health intervention and increasing behavioral health countermeasures.	Adjustment Disorders that cause significant distress or decline in areas including but not limited to work performance, sleep, or interpersonal dynamics, and require long-term pharmacologic therapy (minimum 6 months) and/or behavioral health intervention.	BHP - Adjustment Reaction		
ICL14	BHP - ANXIETY	Acute anxiety or mild panic symptoms caused by situational factors (e.g. burnout, work overload, performance pressure, significant events) that alleviates without any impact to the mission or personal life. It may require pharmacological therapy PRN, behavioral health intervention and/or increased behavioral health countermeasures.	Anxiety Disorders or severe panic symptoms causing significant distress or decline in areas including but not limited to work performance, sleep and interpersonal dynamics. The condition requires long-term pharmacologic therapy (minimum 6 months), and/or behavioral health intervention.	BHP - Panic Symptoms		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL15	BHP - DEPRESSION	Transient apathy, low-motivation, irritability and/or disturbance of mood that resolves without any impact to the mission or personal life and/or requires as needed behavioral health intervention and increased behavioral health countermeasures.	A Depressive Disorder causing significant distress or decline in areas including but not limited to work performance, sleep, and interpersonal dynamics. The condition may also include recurrent suicidal ideation. The Depressive Disorder persists and requires pharmacologic therapy (minimum 6 months) and/or behavioral health intervention; may be treatment resistant; or may result in suicide attempt.	BHP - Apathy BHP - Low Motivation BHP - Irritability BHP - Mood Disturbance		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL16	BHP - GRIEF REACTION	A grief reaction that resolves within one year without any significant impact on mood, sleep or interpersonal functioning or need for significant intervention. PRN Sleep aids and/or behavioral health intervention, increased behavioral health countermeasures could be used as treatment options.	Persistent or complicated grief that causes significant difficulty to recover from the loss. This condition causes significant distress or decline in areas including but not limited to work performance, sleep, interpersonal dynamics and requires long-term pharmacologic therapy (minimum 6 months) and/or behavioral health intervention.	BHP - Grief, Complicated		
ICL17	BHP - PSYCHOSIS SECONDARY TO DEPRESSION	An isolated episode secondary to depression, of thoughts and perceptions that are disturbed and difficulty understanding what is real and what is not, which resolves within the day.	Severe psychotic symptomology, secondary to depression, that requires more than one day of pharmacologic therapy, use of restraints, and/or behavioral health intervention. The psychosis may not resolve.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL18	BHP - SLEEP DISTURBANCE	Transient, mild to moderately disturbed sleep (after day 5 of space flight) caused by but not limited to: environmental factors, sleep shifting, poor sleep hygiene and/or exhaustion, that is effectively treated with appropriate crew scheduling/sleep-shifting, sleep aids or behavioral health interventions.	Sleep-Wake Disorders (after day 5 of spaceflight) such as Insomnia Disorder or Circadian Rhythm Sleep-Wake Disorders that are severe or refractory to treatment with appropriate crew scheduling/sleep-shifting, sleep aids and behavioral health interventions.	BHP - Insomnia BHP - Circadian Rhythm-Sleep Wake Disorders		
ICL19	BURN - CHEMICAL EYE	Chemical exposure to the eyes in which tear pH normalizes within a few minutes and no permanent corneal scaring is expected.	Chemical exposure to the eyes in which tear pH does not normalize within a few minutes, or results in significant scarring/ulceration, or that results in intra-ocular pressure changes.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL20	BURN - CHEMICAL SKIN	Chemical exposure to the skin requiring irrigation that causing superficial damage, OR partial thickness damage involving less than 5% TBSA that meets all of the following criteria: i) non-circumferential, ii) does not cross a major joint line, iii) is not at risk for permanent impairment of body part function (e.g. extensive burns to hands, face, perinium, genitals).	Chemical exposure to the skin requiring irrigation that causes partial thickness burns involving greater than 20% TBSA, full thickness burns involving greater than 5% TBSA, or burns that meet any of the following criteria: i) circumferential, ii) crosses a major joint line, iii) threatens to impair body part function.			
ICL21	BURN - MILD, THERMAL	Superficial burns to the skin that resolve without treatment.	Isolated superficial-partial thickness burns to the skin that respond to topical treatments, dressings, and/or NSAIDs/Acetaminophen.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL22	BURN - MODERATE TO SEVERE, THERMAL	Partial thickness burns covering less than 20% TBSA, OR full thickness burns covering less than 5% TBSA that meet the following criteria: i) non-circumferential, ii) does not cross a major joint line, iii) is not at risk for permanent impairment of body part function (e.g. extensive burns to hands, face, perinium, genitals).	Partial thickness burns involving greater than 20% TBSA, full thickness burns involving greater than 5% TBSA, or burns that meet any of the following criteria: any circumferential burn, anything crossing a major joint line, or threatening to impair body part function or full-thickness skin burns.			
ICL23	CEREBROVASCULAR ACCIDENT	A transient ischemic attack (TIA), or mild stroke, with no significant neurologic impairment.	A stroke that causes significant permanent neurologic impairment, negatively affecting mission objectives.	Transient Ischemic Attack		
ICL24	CERUMEN IMPACTION	Cerumen impaction that is easily identified and removed on first attempt.	Cerumen impaction that results in pain, tinnitus, interferes with mission objectives, or requires multiple attempts at removal. (Note "hearing loss" is a separate condition).			
ICL25	CHOKING/OBSTRUCTED AIRWAY	Choking and cough that resolve spontaneously, or obstructed airway that responds to the Heimlich maneuver.	Choking and obstructed airway that requires instrument extraction or advanced life support.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL26	CHOLELITHIASIS/ BILIARY COLIC, ACUTE	A course of uncomplicated biliary colic which resolves spontaneously or causes minimal disturbance requiring only symptomatic pain management.	Acute cholecystitis with likely complications requiring significant pain management, antibiotic administration, and likely definitive surgical management.	Cholecystitis		
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL27 (***REMOVED***)	COLD INJURY - CHILBLAINS/ FROSTBITE	Superficial tissue injury: Acute chilblains, or 1st or 2nd degree frostbite (i.e., change in color, desquamation, serous blistering).	Deep tissue injury: 3rd or 4th degree frostbite (i.e., full thickness injury, hemorrhagic blisters, necrosis, amputation).		**CLiFF Deleted**	**CLiFF Deleted**
ICL28	DENTAL ABSCESS	An abscess that responds to treatment with pain medication and antibiotics.	An abscess that does not respond to oral treatment or topical anesthetic and requires IV antibiotic administration and/or incision/drainage. (The development of sepsis secondary to necrosis is addressed in the condition Sepsis).			
ICL29	DENTAL CROWN LOSS	Loss of crown requiring no intervention (tooth with prior root canal), or recementing (non-root canaled tooth).	Loss of dental crown due to underlying decaying tooth fracture that requires tooth extraction.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL30	DENTAL FILLING LOSS	Loss of a filling without any pain that can wait until return to earth for treatment.	Loss of a filling which requires pain management with analgesics and/or temporary filling.			
ICL31	DENTAL FRACTURE/ EXPOSED PULP	Reversible pulpitis, (pain is controlled by removing the painful stimuli, oral pain reliever, sensitive toothpaste, or by topical anesthetic) OR a fractured tooth (non-crowned) limited to enamel or dentin exposure (not involving the pulp or root).	Irreversible pulpitis, or fractured tooth (non-crowned) involving the pulp or root, that requires oral pain medications and/or injected analgesic.			
ICL32	DENTAL LUXATION/ AVULSION (TOOTH LOSS)	Luxation or avulsion due to trauma with mild pain and bleeding that is easily controlled.	Avulsion due to trauma, with moderate to severe pain that may require narcotic analgesics, bleeding is prolonged beyond 20 minutes.			
ICL33	DISLOCATION - FINGER	A finger dislocation that is easily reduced and has full range of motion after a period of splinting and physical therapy.	A finger dislocation that cannot be reduced (requires surgery), or has persistent decreased ROM after reduction, splinting, and PT.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL34	DISLOCATION - SHOULDER	A shoulder dislocation that is easily reduced, requires immobilization for less than a week, and does not recur.	A shoulder dislocation that meets any of the following criteria: requires sedation for reduction, results in persistent pain despite reduction, recurs, cannot be reduced, results in neurovascular compromise, or requires surgery.			
ICL35	DIVERTICULITIS, ACUTE	An uncomplicated case of diverticulitis that is self-limited or responds to oral or IV antibiotics.	A complicated case of diverticulitis (i.e., abscess, perforation, fistula, obstruction), requiring IV antibiotics and/or percutaneous or surgical intervention.			
ICL36 ***(REMOVED And DIVIDED)***	DUST EXPOSURE - LUNAR	Lunar dust causing transient symptoms in the eyes, skin and respiratory tract that respond to conservative management.	Lunar dust exposure that leads to sustained pulmonary symptoms requiring greater than 1 week of treatment.	Dust Exposure (Lunar) - Pneumonitis	**CLiFF Divided, then Deleted**	**CLiFF Divided, then Deleted**
ICL36A	DUST EXPOSURE - LUNAR (SURFACE EVA)	Lunar dust causing transient symptoms in the eyes, skin and respiratory tract that respond to conservative management (Surface EVA exposure ONLY)	Lunar dust exposure that leads to sustained pulmonary symptoms requiring greater than 1 week of treatment. (Surface EVA exposure ONLY)	Dust Exposure (Lunar) - Pneumonitis		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL36B	DUST EXPOSURE - LUNAR (EVA HABITAT)	Lunar dust causing transient symptoms in the eyes, skin and respiratory tract that respond to conservative management (EVA Habitat exposure ONLY)	Lunar dust exposure that leads to sustained pulmonary symptoms requiring greater than 1 week of treatment. (EVA Habitat exposure ONLY)	Dust Exposure (Lunar) - Pneumonitis		
ICL37	EBULLISM	~~E~~bullism not requiring any respiratory support and not leading to mission impacting long term neurologic deficits.	Ebullism requiring prolonged respiratory support and/or resulting in mission impacting neurologic deficits.			
ICL38	EPISTAXIS	An anterior nosebleed that resolves with minimal or no treatment.	A posterior nosebleed that requires nasal packing and possibly surgical treatment.			
ICL39	EVA RELATED DECOMPRESSION SICKNESS	Type I DCS with mild to moderate pain in a isolated single joint that resolves spontaneously or with treatment.	Severe joint pain, multiple joints with pain, or migrating joint pain, AND/OR Type II DCS with CNS (spotted vision, slurred speech, coordination difficulty, loss of sensation, headache, seizures, unconsciousness) or cardiopulmonary involvement (chest pain, cough, shortness of breath).			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL40	EVA RELATED DEHYDRATION	Dehydration from EVA that responds to oral rehydration.	Dehydration from EVA that requires intravenous volume repletion or interferes with future EVAs.			
ICL41	EVA RELATED FINGERNAIL DELAMINATION	Mild to moderate nail bed trauma with partial onycholysis that responds to treatment.	Severe nail bed trauma causing onycholysis and/or nail loss despite treatment.	Onycholysis		
ICL42	EVA RELATED HAND INJURY	Category 1: Abrasions sustained secondary to repetitive hand movements within the EVA suit.	Category 2: Hand/finger pain, fatigue, and/or swelling secondary to repetitive use of the hands and fingers in EVA suit.		This condition has Category 1 and Category 2 definitions instead of best and worst case definitions. Category 1 Definition: Abrasions sustained secondary to repetitive hand movements within the EVA suit.	This condition has Category 1 and Category 2 definitions instead of best and worst case definitions. Category 2 Definition: Hand/finger pain, fatigue, and/or swelling secondary to repetitive use of the hands and fingers in the EVA suit.
ICL43	EVA RELATED HEAT ILLNESS	Heat cramps, or heat exhaustion responsive to stopping activity and hydration.	Heat stroke (body core temperature > 40°C).	EVA Related - Heat cramps EVA Related - Heat Exhaustion EVA Related - Heat Stroke		
ICL44	EVA RELATED PARESTHESIA	Mild paresthesia or local pain from a pressure or EVA suit pressure point, with tingling, numbness, and/or pain that resolves spontaneously.	Moderate to severe paresthesia and/or localized pain from a pressure or EVA suit pressure point that may require treatment with analgesics and/or steroids.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL45	EVA RELATED SHOULDER INJURY	Suit related overuse injury or Grade I or II strain/sprain (minimal or partial muscle or ligamentous tearing) in which symptoms can be readily managed with oral or topical medications and supportive care (physical therapy is encouraged).	Suit related overuse injury or Grade III strain/sprain (full thickness muscle or ligamentous tearing), instability, or suspected labral tear that requires additional treatment. Physical therapy is mandatory.	Shoulder - Labral Tear		
ICL46	EVA RELATED SUIT CONTACT INJURY	Contusions, abrasions, friction injuries (blister, rash, chaffing) that resolve spontaneously. (Note this is exclusive of EVA Related Hand Injuries).	Contusions, abrasions, friction injuries (blister, rash, chaffing) that require treatment. (Note this is exclusive of EVA Related Hand Injuries).	EVA related - Skin blister EVA related - Skin Chaffing EVA related - Contusions		
ICL47	EYE - RETINAL INJURY	A retinal tear, burn, or detachment without involvement of the macula (central vision and visual acuity are preserved).	Worst case scenario is defined as a retinal tear, burn, or detachment with involvement of the macula (central vision and visual acuity may be severely reduced).	Eye - Retinal Tear Eye - Retinal Burn Eye -Retinal Detachment		
ICL48	EYE FOREIGN BODY	A foreign body that is easily removed and leaves no damage or minimal damage (e.g., rust ring), or a scleral laceration which has minimal effect on vision.	A penetrating or perforating foreign body resulting in ruptured globe, hyphema, corneal laceration, or other sequelae that effect vision.	Eye - Ruptured Globe Eye - Hyphema Eye - Corneal Laceration Eye - Scleral Laceration		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL49	EYE IRRITATION/CORNEAL ABRASION/ULCERATION	Vision sparing dry/irritated eyes responsive to lubrication, or corneal abrasion not requiring treatment.	Corneal abrasion requiring treatment, or corneal ulceration, which has the potential to result in a permanent impairment of vision.	Eye - Dry Eyes		
ICL50	EYELID AND ANTERIOR EYE INFECTION	Mild eyelid infection or bacterial/viral conjunctivitis that may require symptomatic treatment.	Moderate or severe eye infection which requires antibiotic or antiviral treatment.			
ICL51	FRACTURE - ARM	A closed, non-comminuted, non-segmented, non-displaced, or minimally displaced fracture resulting in no neurovascular compromise to the affected limb.	A fracture that is: open, comminuted, segmented, moderately to severely displaced, intra-articular, or results in neurovascular compromise to the affected limb, likely requiring surgical intervention.	Fracture - Humerus Fracture- Elbow (radial head / supracondylar / olecranon fracture) Fracture - Radius (excluding radial head) Fracture - Ulna (excluding olecranon)		
ICL52	FRACTURE - CERVICAL SPINE	A non-displaced fracture with no dislocation, and mild to moderate pain that responds to analgesics and conservative treatment.	A displaced fracture or dislocation resulting in spinal instability, severe pain, or requiring surgery. (Spinal cord injury covered by "spinal cord injury.")			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL53	FRACTURE - DISTAL LEG	A closed, non-comminuted, non-segmented, non-displaced, or minimally displaced fracture resulting in no neurovascular compromise to the affected limb.	A fracture that is: open, comminuted, segmented, moderately to severely displaced, intra-articular, or results in neurovascular compromise to the affected limb, likely requiring surgical intervention.	Fracture - Knee Fracture - Tibial Shaft Fracture - Proximal Fibular ~~Fracture - LE Stress~~ Fracture - Pilon	Updated to remove stress fractures and keep only traumatic fractures	Updated to remove stress fractures and keep only traumatic fractures
ICL54	FRACTURE - FEMUR	A closed, non-comminuted, non-segmented, non-displaced, or minimally displaced fracture resulting in no neurovascular compromise to the affected limb.	A fracture that is: open, comminuted, segmented, moderately to severely displaced, intra-articular, or results in neurovascular compromise to the affected limb, likely requiring surgical intervention.			
ICL55	FRACTURE - HAND	A closed, non-comminuted, non-segmented, non-displaced, or minimally displaced fracture resulting in no neurovascular compromise to the affected limb.	A fracture that is: open, comminuted, segmented, moderately to severely displaced, intra-articular, or results in neurovascular compromise to the affected limb, likely requiring surgical intervention.	Fracture - Finger Fracture - Thumb Fracture - Metacarpal		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL56	FRACTURE - WRIST	A closed, non-comminuted, non-segmented, non-displaced, or minimally displaced fracture resulting in no neurovascular compromise to the affected limb.	A fracture that is: open, comminuted, segmented, moderately to severely displaced, intra-articular, or results in neurovascular compromise to the affected limb, likely requiring surgical intervention.	Fracture - Scaphoid Fracture - Lunate Fracture - Triquetrum Fracture - Trapezoid Fracture - Trapezium Fracture - Capitate Fracture - Hamate Fracture - Pisiform		
ICL57	FRACTURE-THORACIC/LUMBAR SPINE	A non-displaced fracture with no dislocation, and mild to moderate pain that responds to analgesics and conservative treatment.	A displaced fracture or dislocation resulting in severe pain, spinal instability, or requiring surgery. (Spinal cord injuries covered in category "Spinal Cord Injury.")			
ICL58	GASTRITIS/REFLUX/ ESOPHAGITIS	Mild indigestion, most likely due to gastro-esophageal reflux (GERD), esophagitis, or gastritis, that resolves with minimal or no treatment.	Moderate or severe indigestion, including duodenal and/or gastric ulceration, either requiring prolonged treatment, or leading to complications such as gastrointestinal bleeding.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL59	GASTROENTERITIS/ ACUTE DIARRHEA	An uncomplicated course of gastroenteritis/acute diarrhea which resolves spontaneously or causes minimal disturbance; with mild nausea/vomiting, diarrhea, or abdominal pain requiring only symptomatic treatment.	A severe course of gastroenteritis/acute diarrhea, requiring parenteral re-hydration, or refractory to treatment.	GI - Indigestion GERD GI Ulcer - Duodenal GI Ulcer - Gastric GI bleed (upper)		
ICL60	GLAUCOMA, ACUTE ANGLE-CLOSURE	A mild unilateral angle-closure glaucoma that responds to topical and systemic treatment.	Bilateral angle-closure glaucoma with intraocular pressure that does not respond to topical and systemic treatment and poses risk for irreversible blindness.			
ICL61	GRAVITY WELL - NEUROVESTIBULAR DISTURBANCE	Gravity well sensorimotor Neurovestibular disturbance that results in mild balance deficits or orientation difficulty but does not prevent the operation of machinery or piloting.	Gravity well sensorimotor Neurovestibular disturbance that results in moderate or severe balance deficits and orientation difficulty and prevents the operation of machinery or piloting.			
ICL62	GRAVITY WELL - ORTHOSTATIC INTOLERANCE	Mild orthostatic intolerance, related to gravity, that spontaneously resolves.	Orthostatic intolerance, related to gravity, requiring IV fluids or resulting in syncopal episode.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL63	HEADACHE	An uncomplicated headache (unrelated to space adaptation), which resolves spontaneously or with first line medications or non-pharmacologic treatment. (Note this is exclusive of headaches secondary to CO2, which is covered by "Headache - CO2" condition).	A headache refractory to second line-medications and non-pharmacologic treatments, requiring additional interventions. (Note this is exclusive of headaches secondary to CO2, which is covered by "Headache - CO2" condition).			
ICL64	HEADACHE - CO2 INDUCED	A CO2-induced headache, which resolves spontaneously or with symptomatic treatment and does not impact mission objectives.	Severe CO2-induced headache that is either refractory to initial treatment or impacts mission objectives.			
ICL65	HEARING LOSS	A reversible or conductive hearing loss that manifests as a Mission Significant Threshold Shift (M-STS) that resolves within 30 days and does not impair communication.	A sensorineural or non-reversible hearing loss that manifests as an M-STS lasting greater than 30 days or impairs communication.	Hearing loss - Sensorineural Hearing Loss - Conductive		
ICL66	HEARING LOSS - NOISE-RELATED	A Mission Significant Threshold Shift (M-STS) that resolves within 30 days and does not impair communication.	A M-STS that lasts greater than 30 days or that impairs communication.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL67	HEMORRHOIDS	Symptomatic hemorrhoids that respond to topical treatment and dietary and fluid modification (Stages I and II).	Moderate or severe hemorrhoids refractory to initial treatment, or with excessive bleeding (Stages III and IV).			
ICL68	HERPES ZOSTER REACTIVATION (SHINGLES)	An uncomplicated course of herpes zoster over several days which causes minimal disturbance with localized pain and may require treatment with antiviral and/or pain medications.	A prolonged course of herpes zoster accompanied by symptoms of either persistent disruptive pain, e.g. post herpetic neuralgia (PHN), or ocular and neurological complications (peripheral motor neuropathy, Ramsay Hunt syndrome, or HZ ophthalmicus).			
ICL69 (***REMOVED***)	HYPOTHERMIA	Mild hypothermia requiring passive rewarming.	Moderate to severe hypothermia requiring active rewarming and/or intensive care treatment.		**CLiFF Deleted**	**CLiFF Deleted**
ICL70	MOUTH ULCER	A mouth ulcer causing minimal discomfort that may require topical treatment.	A mouth ulcer with moderate to severe pain that requires-oral pain medication or for the crewmember to be on a soft or liquid diet.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL71	NEPHROLITHIASIS	A renal stone that responds to conservative treatment (e.g. analgesics and hydration).	A renal stone that does not respond to conservative treatment (e.g., requires lithotripsy or surgical treatment).			
ICL72	NEUROPATHY - CENTRAL, IMPINGEMENT RELATED	Neuropathy due to nerve impingement that resolves spontaneously (i.e., pinched nerve) or with symptomatic treatment (this excludes peripheral impingement syndromes).	Persistent neuropathy due to impingement that requires nerve-modulating agents, steroids, or surgical intervention. (This excludes peripheral impingement syndromes)	Neuropathy - Lateral femoral cutaneous nerve entrapment Neuropathy - Sciatica/piriform syndrome Neuropathy - Brachial plexus injury Neuropathy - Pain related to nerve root impingement/disc herniation		
ICL73	OTITIS EXTERNA	Otitis externa resolving with one course of antibiotics. Associated pain is controlled with non-opioid analgesics.	Otitis externa that is accompanied by pain that cannot be controlled with non-opioid analgesics or requires more than one course of antibiotics.			
ICL74	OTITIS MEDIA	Acute otitis media that resolves with a single course of antibiotics and responds to non-opioid analgesics.	Severe acute otitis media that is accompanied by pain that cannot be controlled with non-opioid analgesics, causes hearing loss, or requires more than one course of-antibiotics.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL75	PANCREATITIS, ACUTE	An uncomplicated acute pancreatitis which resolves with minimal intervention (observation while NPO, IV fluid hydration, and minimal pain management). (Note cholecystitis is covered by condition CHOLELITHIASIS/ BILIARY COLIC, ACUTE)	Complicated acute pancreatitis with severe systemic manifestations (i.e.,-acute renal failure, necrotizing pancreatitis) requiring standard (pain management and aggressive IV hydration) as well as more advanced interventions (e.g., IV antibiotics, parenteral nutrition). (Note cholecystitis is covered by condition CHOLELITHIASIS/BILIARY COLIC, ACUTE)			
ICL76	PREGNANCY, RISK FOR	Vaginal intercourse involving a male and pre-menopausal female crewmember in which emergency contraception is used to prevent pregnancy. It is also considered a BC scenario if a crewmember involved is using a long-acting reversible contraceptive (LARC) or undergone procedure for permanent sterility.	Vaginal intercourse involving a male and pre-menopausal female crewmember who is not using a long-acting reversible contraceptive (LARC) or has not undergone a procedure for permanent sterility AND emergency contraception was either not used or was not successful.		Vaginal intercourse involving a male and pre-menopausal female crewmember in which emergency contraception is used to prevent pregnancy. It is also considered a best-case scenario if a crewmember involved is using a long-acting reversible contraceptive (LARC) or undergone procedure for permanent sterility.	Vaginal intercourse involving a male and pre-menopausal female crewmember who is not using a long-acting reversible contraceptive (LARC) or has not undergone a procedure for permanent sterility AND emergency contraception was either not used or was not successful.

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL77	PROSTATITIS, ACUTE	Prostatitis that responds to treatment with analgesics and antibiotics.	Prostatitis that requires more than one course of antibiotics or develops an abscess.	Prostatic Abscess	Prostatitis that responds to treatment with analgesics and antibiotics.	Prostatitis that requires more than one course of antibiotics, develops an abscess, or progresses to severe sepsis.
ICL78	RASH, SPACEFLIGHT ASSOCIATED	Mild to moderate and uncomplicated skin rash that responds to topical treatment.	Moderate to severe skin rash, covering an extensive area and that requires more than 5-7 days of topical treatment, requires a course of oral or IV medications, or is refractory to treatment.			
ICL79 ***REMOVED***	REACTIVE AIRWAY	Reactive airway that responds to inhalers, and/or steroids without requiring hospitalization. (Note this does not include infectious causes which are covered by the condition "Respiratory Tract Infection - Lower.")	Reactive airway requiring hospitalization, but not requiring intubation (see "Respiratory Failure"). (Note this does not include infectious causes which are covered by the condition "Respiratory Tract Infection - Lower.")		~~Reactive airway that responds to inhalers, and/or steroids without requiring hospitalization.~~ **CLiFF Deleted**	~~Reactive airway requiring hospitalization, but not requiring intubation (see "Respiratory Failure").~~ **CLiFF Deleted**
ICL80	RESPIRATORY FAILURE	Category 1 is acute respiratory distress syndrome or respiratory failure secondary to infection (viral or bacterial).	Category 2 is acute respiratory distress syndrome or respiratory failure secondary to any of the following: airway burns, pneumonitis, reactive airway disease, or toxic inhalation exposure.	Respiratory Distress Syndrome, Acute		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL81	RESPIRATORY TRACT INFECTION - LOWER	Influenza-like illness, or viral bronchitis that resolves with symptomatic treatment.	Bacterial supra-infected influenza-like illness or bronchitis or bacterial pneumonia, that requires treatment but does not result in ARDS or respiratory failure.	Respiratory Tract Infection (Lower) - Influenza Respiratory Tract Infection (Lower) - Bronchitis, Viral Respiratory Tract Infection (Lower) - Pneumonia, Bacterial Respiratory Tract Infection (Lower) - Coronavirus	Influenza-like illness, or viral bronchitis that resolves with symptomatic treatment.	Bacterial suprainfected influenza-like illness or bronchitis or bacterial pneumonia, that requires treatment.
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL82	RESPIRATORY TRACT INFECTION - UPPER	Uncomplicated viral or allergic rhinosinusitis, non-strep pharyngitis, or the common cold that are treated successfully with first line treatment.	Bacterial rhinosinusitis requiring antibiotics.	Respiratory Tract Infection (Upper) - Rhinitis, Acute Respiratory Tract Infection (Upper) - Sinusitis, Acute Respiratory Tract Infection (Upper) - Pharyngitis, Non-strep		
ICL83	SEIZURES	A single seizure that resolves spontaneously or responds to drug therapy and does not recur.	Status epilepticus (a seizure lasting longer than 5 minutes, or ≥2 discrete seizures between which there is incomplete recovery of consciousness).	Status Epilepticus		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL84	SEPSIS	Meeting SIRS criteria, but responsive to intervention.	Septic shock (e.g., requiring vasopressors, end organ failure).	Shock - Sepsis		
ICL85	SHOCK - CARDIOGENIC	INTENTIONALLY LEFT BLANK, only WC scenario for this condition.	Life-threatening circulatory collapse requiring extensive support measures.	Neurogenic Shock will be included in this when precursor injuries make future iterations of the list.		Life-threatening circulatory collapse requiring extensive support measures. This condition is a presumed to be post-myocardial infarction unrelated to other conditions such as toxic ingestion, sepsis, etc.
ICL86	SKIN ABRASION	Mild abrasion(s) resolving spontaneously or requiring minimal intervention. (Note EVA related skin abrasion is covered by "EVA Related Contact Injury OR EVA Related Hand Injury" and this is exclusive of "Cellulitis").	Moderate to severe abrasion(s) requiring additional intervention. (Note EVA related skin abrasion is covered by "EVA Related Contact Injury OR EVA Related Hand Injury" and this is exclusive of "Cellulitis").			
ICL87	SKIN INFECTION - BACTERIAL	A bacterial skin infection that resolves without treatment, or treatment with topical or a single course of oral antibiotics.	A moderate or severe bacterial skin infection requiring a second course of oral antibiotics, a course of intramuscular or intravenous antibiotics, or that is refractory to treatment. (Note necrotizing fasciitis is a separate condition).	Cellulitis, Erysipelas, Folliculitis, Furuncles, Impetigo, and Erythrasma		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL88	SKIN INFECTION - VIRAL/FUNGAL	Mild viral or fungal skin infection, that resolves without treatment, or minimal treatment with topical or a single course of oral antivirals or antifungals.	Moderate to severe viral or fungal skin infection that could require a second course of antivirals/antifungals or could be refractory to treatment.			
ICL89	SKIN LACERATION	An uncomplicated, linear, laceration that is not under significant tension with minimal or no foreign body contamination that heals spontaneously or requires a single layer closure.	A laceration meeting one or more of the following criteria: complex, stellate, multi-layer closure, under significant tension, and/or involving foreign body contamination requiring exploration and removal.			
ICL90	SMALL BOWEL OBSTRUCTION	Small bowel obstruction which responds to conservative medical treatment such as bowel rest, fluid resuscitation, analgesics and NG tube.	Small bowel obstruction that is not responsive to conservative management and requires surgical intervention.			
ICL91	SPACE ADAPTATION - BACK PAIN	Back awareness to mild back discomfort.	Moderate to severe back pain.			
ICL92	SPACE ADAPTATION - CONSTIPATION	Symptomatic complaints of constipation, requiring treatment with hydration and dietary changes.	Symptomatic complaints of constipation that do not respond to initial treatment and require medication and/or disimpaction.	Fecal Impaction		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL93	SPACE ADAPTATION - EPISTAXIS	An anterior nosebleed that resolves with minimal or no treatment.	A posterior nosebleed that requires nasal packing and possibly surgical treatment.			
ICL94	SPACE ADAPTATION - HEADACHE	An uncomplicated course of space adaptation syndrome-related headache, which resolves spontaneously or with minor symptomatic treatment.	A severe space adaptation related headache poorly responsive to available treatment.			
ICL95	SPACE ADAPTATION - INSOMNIA	Insomnia occurring within the first 5 days of spaceflight that is mild and is effectively treated with appropriate crew scheduling/sleep-shifting and sleep-aids.	Insomnia within the first 5 days of spaceflight that is severe or refractory to treatment with appropriate crew scheduling/sleep-shifting and sleep-aids.			
ICL96	SPACE ADAPTATION - NASAL CONGESTION	Nasal congestion that resolves spontaneously.	Nasal congestion requiring treatment.			
ICL97	SPACE ADAPTATION - SPACE MOTION SICKNESS	Space motion sickness including mild to moderate symptoms (e.g., loss of appetite, malaise, stomach awareness, 2 or fewer episodes of emesis, resolves within 72 hours, causes no or minimal performance decrement).	SMS with severe and persistent symptoms (e.g., need to keep head from moving, greater than 2 episodes of emesis, significant performance decrement, persists for greater than 72 hours).			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL98	SPACE ADAPTATION - URINARY RETENTION	Urinary retention that resolves spontaneously or with a single straight catheterization.	Urinary retention that requires repeated straight or indwelling catheter.		Urinary retention that resolves spontaneously or requires one-time straight catheterization for resolution.	Urinary retention that requires repeated straight catheterization or indwelling catheter.
ICL99	SPACE ADAPTATON - URINARY INCONTINENCE	An uncomplicated course of urinary incontinence which resolves by itself and/or causes minimal discomfort.	INTENTIONALLY LEFT BLANK, only BC scenario for this condition.		The best case scenario is defined as having an uncomplicated course of urinary incontinence which resolves by itself or causes minimal discomfort.	Not applicable.
ICL100	SPACEFLIGHT ASSOCIATED NEURO-OCULAR SYNDROME (SANS)	Visual acuity changes and/or papilledema grades 0-2.	Visual acuity changes and papilledema grades 3 or above.		>55um to 200um change in total retinal thickness (TRT), presence of any choroidal folds, or visual acuity change >0.75 diopters in either eye measured during or post flight.	>200um change in total retinal thickness (TRT), choroidal folds overlying the fovea, or visual field defects with blind spots
ICL101	SPRAIN/STRAIN - BACK	A Grade I or II strain/sprain in which there is minimal or partial muscle or ligamentous tearing.	A Grade III strain/sprain in which there is full thickness muscle or ligamentous tearing, and/or instability.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL102	SPRAIN/STRAIN - LOWER EXTREMITY	A Grade I or II strain/sprain in which there is minimal or partial muscle or ligamentous tearing.	A Grade III strain/sprain in which there is full thickness muscle or ligamentous tearing, and/or instability.	Sprain/Strain - Hip Sprain/Strain - Knee Sprain/Strain - Ankle Sprain/Strain - Foot Sprain/Strain - Medial gastrocnemius muscle strain Sprain/Strain - Achilles tendon injury		
ICL103	SPRAIN/STRAIN - NECK	A Grade I or II strain/sprain in which there is minimal or partial muscle or ligamentous tearing.	A Grade III strain/sprain in which there is full thickness muscle or ligamentous tearing, and/or instability.			
ICL104	SPRAIN/STRAIN - UPPER EXTREMITY	A Grade I or II strain/sprain in which there is minimal or partial muscle or ligamentous tearing.	A Grade III strain/sprain in which there is full thickness muscle or ligamentous tearing, and/or instability.	Sprain/Strain - Shoulder Sprain/Strain - Elbow Sprain/Strain - Wrist Sprain - Finger Finger tendon injury		
ICL105	STREPTOCOCCAL PHARYNGITIS	Uncomplicated streptococcal pharyngitis that resolves spontaneously.	A peritonsillar abscess requiring IV antibiotics and possible incision/drainage.	Peritonsillar Abscess	Uncomplicated streptococcal pharyngitis that resolves spontaneously or with oral antibiotics.	A peritonsillar abscess requiring IV antibiotics and possible incision/drainage.

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL106	SUDDEN CARDIAC ARREST	A witnessed arrest with a cardiac rhythm of ventricular tachycardia or ventricular fibrillation, responsive to airway management, defibrillation, and CPR.	An unwitnessed arrest, a witnessed arrest with a cardiac rhythm other than V-Tach/V-Fib, or an arrest that is non-responsive to airway management, defibrillation, and CPR.			
ICL107	TENDINOPATHY/ ENTHESOPATHY/ BURSITIS/OVER-USE INJURIES - LOWER EXTREMITY	A tendinopathy/enthesopathy, bursitis, or overuse injury which can be managed symptomatically (e.g., rest, non-opioid analgesics, physical therapy) and does not impact mission objectives.	A tendinopathy/ enthesopathy, bursitis, or overuse injury which requires treatment (e.g., corticosteroid injection, dry needling, physical therapy, nitroglycerin patches), or impacts mission objectives. Elective surgery may be necessary post-mission.			
ICL108	TENDINOPATHY/ ENTHESOPATHY /BURSITIS/OVER-USE INJURIES - UPPER EXTREMITY	A tendinopathy/enthesopathy, bursitis, or overuse injury which can be managed symptomatically (e.g., rest, non-opioid analgesics, physical therapy) and does not impact mission objectives.	A tendinopathy/enthesopathy, bursitis, or overuse injury which requires treatment (e.g., corticosteroid injection, dry needling, physical therapy, nitroglycerin patches), or impacts mission objectives. Elective surgery may be necessary post-mission.			

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL109	TOXIC DERMAL EXPOSURE	Dermal exposure to an irritant substance resulting in inflammation/irritation that responds to treatment.	Dermal exposure to a corrosive substance resulting in cell death, ulceration, leading to permanent scarring.	Toxic Dermal Exposure - Can be applied to any substance in theory		
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL110	TOXIC INHALATION EXPOSURE	An exposure to an inhaled toxin with symptoms that are self-limited or respond to symptomatic treatment. (Note combustion products are covered by a separate condition).	An exposure to an inhaled toxin that requires treatment but does not result in ARDS/Respiratory Failure (see "Respiratory Failure"). (Note combustion products are covered by condition "COMBUSTION PRODUCT INHALATION EXPOSURE").	Toxic Inhalation Exposure - Can be applied to any substance in theory	An exposure to an inhaled toxin with symptoms that are mild and self-limited. (Note combustion products are covered by a separate condition).	An exposure to an inhaled toxin that requires symptomatic treatment. (Note combustion products are covered by condition "COMBUSTION PRODUCT INHALATION EXPOSURE").

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL111	TOXIC INHALATION EXPOSURE - COMBUSTION PRODUCTS	Inhalation of combustion products resulting in direct toxic damage to tissue or interferes with enzymatic processes, excluding cyanide, responding to supportive treatment.	Inhalation of combustion products resulting in direct toxic damage to tissue or interferes with enzymatic processes, including cyanide, requiring additional treatment. (Note ARDS/Respiratory failure are covered by condition "Respiratory Failure.")	Toxic Inhalation Exposure - Carbon Monoxide poisoning Toxic Inhalation Exposure - Cyanide Poisoning Toxic Inhalation Exposure -Nitrogen Dioxide Toxic Inhalation Exposure - Sulfur Dioxide Toxic Inhalation Exposure - Hydrocarbons	Inhalation of combustion products resulting in direct toxic damage to tissue or interferes with enzymatic processes, excluding cyanide, responding to supportive treatment.	Inhalation of combustion products resulting in direct toxic damage to tissue or interferes with enzymatic processes, including cyanide, requiring additional treatment.
ICL112	TRAUMA - ABDOMINAL INJURY (BLUNT)	Blunt abdominal trauma resulting in localized pain/discomfort and/or ecchymosis, with no hollow or solid organ involvement and no evidence of peritonitis or bleeding, requiring only supportive treatment.	Blunt abdominal trauma that causes abdominal visceral damage with possible secondary complications of internal bleeding, mesenteric injury, or peritonitis. (Note Sepsis and Traumatic Hypovolemic Shock are separate conditions).	Trauma (Blunt) - Peritonitis Trauma (Blunt) - Mesenteric Injury	Blunt abdominal trauma resulting in localized pain/discomfort and/or ecchymosis, with no hollow or solid organ involvement and no evidence of peritonitis or bleeding, requiring only supportive treatment.	Blunt abdominal trauma that causes abdominal visceral damage with possible secondary complications of internal bleeding, mesenteric injury, or peritonitis.

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL113	TRAUMA - CHEST INJURY (BLUNT)	Mild or moderate blunt chest injury resulting in localized pain/discomfort and/or ecchymosis, requiring supportive treatment.	Severe blunt chest trauma that causes damage of the internal chest organs with secondary complications (e.g., hemo-thorax/mediastinum/pericardium, pneumo-thorax/mediastinum/pericardium, diaphragmatic rupture, rib fractures).	Trauma (Blunt) - Hemothorax Trauma (Blunt) - Hemomediastinum Trauma (Blunt) - Hemopericardium		
ICL114	TRAUMA - MINOR HEAD	Head trauma resulting in a concussion that impacts mission objectives for less than 2 weeks (this includes concussive symptoms caused by non-surgical intracranial bleeds meeting the above criteria).	Head trauma resulting in post-concussive syndrome interfering with mission objectives or requiring medications for longer than 2 weeks.	Concussion Post-Concussive Syndrome Intracranial Bleed (Non-surgical)		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL115	TRAUMA - SEVERE HEAD	Severe non-surgical TBI (initial GCS < 9) including diffuse axonal injury or other persistent vegetative state	severe surgical TBI (GCS < 9) including Epidural Hematoma, extensive subdural hematoma, swelling causing risk of imminent herniation, or open skull fracture	Traumatic Brain Injury Intracranial Hematoma, Epidural Intracranial Hematoma, Subdural Diffuse Axonal Injury	This condition does not have a "best-case" and "worst-case" scenario. Rather, it has a "Category 1" scenario encompassing severe non-surgical TBI resulting in diffuse axonal injury (DAI) or persistent vegetative state (PVS) and a "Category 2" scenario encompassing severe surgical TBI, including intracranial bleeding, risk of herniation, and open skull fracture. Category 1 Scenario Definition: Severe non-surgical TBI (initial GCS < 9) including diffuse axonal injury or other persistent vegetative state	This condition does not have a "best-case" and "worst-case" scenario. Rather, it has a "Category 1" scenario encompassing severe non-surgical TBI resulting in diffuse axonal injury (DAI) or persistent vegetative state (PVS) and a "Category 2" scenario encompassing severe surgical TBI, including intracranial bleeding, risk of herniation, and open skull fracture. Category 2 Scenario Definition: Severe surgical TBI (GCS < 9) including Epidural Hematoma, extensive subdural hematoma, swelling causing risk of imminent herniation, or open skull fracture
ICL116	TRAUMATIC HYPOVOLEMIC SHOCK	Traumatic hypovolemic shock resulting in signs of end organ compromise that resolves with fluid resuscitation.	Traumatic hypovolemic shock resulting in signs of end organ compromise that fails to resolve with fluid resuscitation or requires blood transfusion.	Acute Hypovolemia		
ICL117	URINARY TRACT INFECTION	Urinary tract Infection (UTI) responsive to oral antibiotics.	UTI or pyelonephritis requiring IV antibiotics.	Pyelonephritis		

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL118	VAGINAL YEAST INFECTION	Uncomplicated vulvovaginal candidiasis, with mild to moderate, sporadic, or infrequent vulvar irritation, including itching and discomfort of the vulvar skin and vaginal epithelium, vaginal discharge, and/or discomfort with voiding which responds to all azole treatment regimens including single-dose oral, and intra-vaginal therapy.	Complicated, severe, or recurrent vulvovaginal candidiasis requiring extended oral treatment.			
ICL119	VENOUS THROMBOEMBOLISM	Thrombus in situ (DVT) without pulmonary embolism.	Pulmonary embolism.	Deep Vein Thrombosis Pulmonary Embolism		
ICL120 (***REMOVED***)	VERTEBRAL DISC DISORDER	Acute low back pain that resolves spontaneously and does not interfere with mission objectives.	Chronic low back pain requiring treatment for more than 3 months. (Note that sciatica is covered by the condition "Impingement related neuropathy")	Back Pain, Acute Low Back Pain, Chronic Low	**CLiFF Deleted**	**CLiFF Deleted**

IMPACT ICL 1.0, v1					IMPACT ICL 1.0, v3.2 (Definition Changes)	
ID	**CONDITION**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**	**CNES**	**Best-Case Scenario Definition**	**Worst-Case Scenario Definition**
ICL121 (***REMOVED***)	BHP - SPACEFLIGHT RELATED RELATIONSHIP PROBLEMS	Interpersonal conflict that is either quickly resolved or addressed appropriately. The conflict does not interfere with operations and/or does not create enduring negative impacts to relationships.	Continuous relationship problems (i.e., family, crew, mission support personnel) that cause significant personal stress that interferes with work performance, other relationships, social withdraw, mood, or sleep and has marked negative impact on crew members, crew cohesion as well as on operations. Treatment is increased behavioral countermeasures and counseling.		**CLiFF Deleted**	**CLiFF Deleted**
ICL122	GRAVITY WELL - ENTRY MOTION SICKNESS	Entry motion sickness that results in nausea/vomiting that responds to behavior modifications and/or medications.	Entry motion sickness that results in nausea/vomiting and does not respond to behavior modifications and/or medications.			
ICL123	PREGNANCY, FIRST TRIMESTER	First trimester intrauterine pregnancy inclusive of uncomplicated early pregnancy loss not requiring surgical management.	Ectopic pregnancy OR complicated early pregnancy loss requiring surgical management.			

APPENDIX D MASTER CONDITION LIST (443 CONDITIONS):

Additional 7 conditions created early in the splitting/combining process included for transparency (total 450 conditions).

MCL1	Abdominal wall hernia	MCL36	BHP - Delirium
MCL2	Abnormal uterine bleeding	MCL37	BHP - Depression
MCL3	Acquired ovarian atrophy	MCL38	BHP - Grief reaction
MCL4	Acute Anemia - hypovolemic	MCL 39	BHP - Psychosis secondary to depression
MCL5	Acute coronary syndrome	MCL40	BHP - Sleep disturbance -
MCL6	Acute neuropraxia (e.g., stretched nerve)	MCL41	BHP - Spaceflight related relationship problems
MCL7	Acute radiation syndrome	MCL42	Biliary cirrhosis
MCL8	Acute tubular necrosis	MCL43	Bipolar disorder
MCL9	Adhesive capsulitis	MCL44	Blepharitis
MCL10	Adjustment disorder	MCL45	Benign Paroxysmal Positional Vertigo
MCL11	Allergic reaction (mild to moderate)	MCL46	Breast lump/mass
MCL12	Allergic rhinitis	MCL47	Bullous dermatosis
MCL13	Amyotrophic Lateral Sclerosis	MCL48	Burn - chemical eye
MCL14	Altitude sickness	MCL49	Burn - chemical skin
MCL15	Amyloidosis	MCL50	Burn - moderate to severe, secondary to fire
MCL16	Anal fissure	MCL51	Burn - thermal
MCL17	Anal rectal/polyp	MCL52	Calculus of prostate
MCL18	Anaphylaxis	MCL53	Cardiac conduction abnormalities
MCL19	Angina/myocardial infarction	MCL54	Cataract
MCL20	Aortic aneurysm	MCL55	Celiac disease
MCL21	Aortic dissection	MCL56	Cellulitis
MCL22	Aortic ectasia	MCL57	Cellulitis, periorbital
MCL23	Appendicitis	MCL58	Central sleep apnea
MCL24	Artery stricture	MCL59	Cerebrovascular accident
MCL25	Arthritis, acute	MCL60	Cerumen impaction
MCL26	Aseptic necrosis	MCL61	Chalazion
MCL27	Atrial fibrillation/ atrial flutter	MCL62	Chemical burn
MCL28	Autonomic dysreflexia	MCL63	Chest wall inflammation/ costochondritis
MCL29	Barotrauma (ear/sinus block)	MCL64	Choking/obstructed airway
MCL30	Bartholin's gland abscess	MCL65	Cholangitis
MCL31	Behavioral emergency	MCL66	Cholecystitis/biliary colic, acute
MCL32	Benign neoplasm	MCL67	Chondromalacia patellae
MCL33	Benzodiazepine or opioid overdose	MCL68	Chorioretinitis
MCL34	BHP - Adjustment disorder	MCL69	Choroidal detachment
MCL35	BHP - Anxiety	MCL70	Chronic diarrhea

MCL 71	Cold injury - Chilblains/frostbite	MCL 111	Endocrine - parathyroidism
MCL 72	Complex regional pain	MCL 112	Endocrine - Pituitary adenoma
MCL 73	Corneal dystrophy	MCL 113	Endomyocardial fibrosis
MCL 74	Corneal vascularization	MCL 114	Enthesopathy
MCL 75	Coronary artery aneurysm	MCL 115	Entropion
MCL 76	Coronary artery dissection	MCL 116	Epistaxis
MCL 77	Cracked tooth	MCL 117	Erythema multiforme
MCL 78	Delirium	MCL 118	Erythema nodosum
MCL 79	Dental abscess	MCL 119	Esophageal spasm/inflammation
MCL 80	Dental caries	MCL 120	Esophageal stricture
MCL 81	Dental crown loss	MCL 121	Essential thrombocytopenia
MCL 82	Dental filling loss	MCL 122	EVA (surface) related friction injury
MCL 83	Dental fracture/exposed pulp	MCL 123	EVA eye irritation
MCL 84	Dental luxation/avulsion (tooth loss)	MCL 124	EVA related decompression sickness
MCL 85	Dermatological - Pressure injury	MCL 125	EVA related dehydration
MCL 86	Dermatological - Soft tissue foreign body	MCL 126	EVA related fingernail delamination
MCL 87	Dermatomyositis	MCL 127	EVA related hand injury
MCL 88	Diabetes insipidus	MCL 128	EVA related heat illness
MCL 89	Dislocation - elbow	MCL 129	EVA related lower extremity strain/sprain
MCL 90	Dislocation - finger	MCL 130	EVA related paresthesia
MCL 91	Dislocation - hip / pelvis	MCL 131	EVA related shoulder injury
MCL 92	Dislocation - patella	MCL 132	EVA related skin contusion/hematoma injury
MCL 93	Dislocation - shoulder	MCL 133	EVA related suit contact injury
MCL 94	Dislocation/fracture - Foot/ankle	MCL 134	EVA related suit failure
MCL 95	Disseminated intravascular coagulopathy (DIC)	MCL 135	EVA related upper extremity strain/sprain
MCL 96	Dissociative disorder	MCL 136	Extreme pain of unclear etiology
MCL 97	Diverticulitis, acute	MCL 137	Eye - retinal injury
MCL 98	Dust exposure - lunar	MCL 138	Eye foreign body
MCL 99	Dust exposure - Martian	MCL 139	Eye irritation/abrasion
MCL 100	Dysbaric osteonecrosis	MCL 140	Eye irritation/corneal abrasion/ulceration
MCL 101	Dysmenorrhea	MCL 141	Eye trauma / injury - Eyelid laceration
MCL 102	Ebullism	MCL 142	Eye trauma / injury - Orbital cellulitis
MCL 103	Ectopic beats (Premature ventricular/atrial contractions)	MCL 143	Eye trauma / injury - Orbital Wall Fracture
MCL 104	Elbow - epicondylitis	MCL 144	Eye trauma / injury - Retinal Burn
MCL 105	Elbow -radial head / supracondylar / olecranon fracture	MCL 145	Eye trauma / injury - Retinal Tear
MCL 106	Elbow sprain/strain	MCL 146	Eyelid and anterior eye infection
MCL 107	Electrical injury	MCL 147	Facial trauma - mandibular dislocation
MCL 108	Endocarditis	MCL 148	Facial trauma - mandibular fracture
MCL 109	Endocrine - hyperthyroidism	MCL 149	Facial trauma - maxillary fracture
MCL 110	Endocrine - hypothyroidism	MCL 150	Facial trauma - nasal bone fracture

MCL151	Facial trauma - septal hematoma	MCL191	Genital Concerns - Pregnancy - Threatened abortion
MCL152	Facial trauma - zygomatic fracture	MCL192	Genital Concerns - Sexually Transmitted infection
MCL153	Fasciitis	MCL193	Genital Concerns - Testicular torsion
MCL154	Finger - finger tendon injury	MCL194	Genital Concerns – Tubo-Ovarian Abscess
MCL155	Fingernail hematoma	MCL195	Genital Concerns - Phimosis
MCL156	Foot fracture/dislocation	MCL196	Genital Concerns - Priapism
MCL157	Foot sprain	MCL197	Giant cell arteritis
MCL158	Foot/ankle sprain/strain	MCL198	Gingivitis/periodontitis
MCL159	Fracture - arm	MCL199	Glaucoma, acute angle-closure
MCL160	Fracture - cervical spine	MCL200	Glaucoma/ocular HTN
MCL161	Fracture - compression, thoracic/lumbar spine	MCL201	Glomerulonephritis
MCL162	Fracture - distal leg	MCL202	Gravity Well – Entry sensorimotor/Neurovestibular disturbance
MCL163	Fracture - femur	MCL203	Gravity well - orthostatic intolerance
MCL164	Fracture - hand	MCL204	Headache
MCL165	Fracture - pelvis	MCL205	Headache – Carbon Dioxide induced
MCL166	Fracture - shoulder	MCL206	Hearing loss
MCL167	Fracture - wrist	MCL207	Hearing loss - noise-related
MCL168	Fracture- thoracic/lumbar spine	MCL208	Hemolytic anemia
MCL169	Gastritis/reflux/esophagitis	MCL209	Hemorrhoids
MCL170	Gastroenteritis	MCL210	Herpes zoster reactivation (shingles)
MCL171	Gastroenteritis/acute diarrhea	MCL211	Hidradenitis
MCL172	Gastrointestinal considerations - Diverticulosis	MCL212	Hip / Pelvis - Gluteal Medius tears
MCL173	Gastrointestinal considerations - Gastrointestinal bleed	MCL213	Hip / Pelvis - Lateral femoral cutaneous nerve entrapment
MCL174	Gastrointestinal considerations - Ischemic colitis	MCL214	Hip / Pelvis - Osteitis pubis
MCL175	Gastrointestinal considerations - Peptic Ulcer Disease	MCL215	Hip / Pelvis - Sciatica/piriform syndrome
MCL176	Gastrointestinal considerations - Ulcerative Colitis	MCL216	Hip / Pelvis - Snapping hip
MCL177	Gastrointestinal considerations - Clostridium Difficile	MCL217	Hip / Pelvis - Trochanteric / iliopectineal/iliopsoas bursitis
MCL178	Genital Concerns - Bacterial vaginosis	MCL218	Histiocytosis
MCL179	Genital concerns - endometriosis	MCL219	Humeral Fracture
MCL180	Genital concerns - epididymitis	MCL220	Hyperlipidemia
MCL181	Genital Concerns - Ovarian cysts - ruptured	MCL221	Hypersensitivity angiitis
MCL182	Genital Concerns - Ovarian cysts -hemorrhagic	MCL222	Hypertension
MCL183	Genital Concerns - Ovarian torsion	MCL223	Hypothermia
MCL184	Genital concerns - paraphimosis	MCL224	Irritable Bowel Syndrome
MCL185	Genital concerns - pregnancy - ectopic	MCL225	Impingement syndromes - peripheral
MCL186	Genital Concerns - Pregnancy - Incomplete abortion	MCL226	Inflammatory disease of breast
MCL187	Genital concerns - pregnancy - intrauterine	MCL227	Influenza
MCL188	Genital Concerns - Pregnancy - Missed abortion	MCL228	Interstitial lung disease
MCL189	Genital Concerns - Pregnancy - Retained products of conception	MCL229	Intussusception
MCL190	Genital Concerns - Pregnancy - Spontaneous abortion	MCL230	Iridocyclitis

MCL231	Iron deficiency	MCL271	Neoplastic - liver carcinoma
MCL232	Iron deficiency anemia	MCL272	Neoplastic - Lung carcinoma
MCL233	Idiopathic Thrombocytopenic Purpura	MCL273	Neoplastic - Multiple myeloma
MCL234	Joint ankylosis/ankylosis spondylitis	MCL274	Neoplastic - Non-Hodgkin's lymphoma
MCL235	Kidney / Urinary - obstructive / Benign Prostatic Hyperplasia	MCL275	Neoplastic - Oropharyngeal carcinoma
MCL236	Knee - Knee fracture	MCL276	Neoplastic - Ovarian carcinoma
MCL237	Knee - Pes anserine, prepatellar bursitis	MCL277	Neoplastic - Pancreatic carcinoma
MCL238	Knee Sprain/Strain	MCL278	Neoplastic - Penile carcinoma
MCL239	Labyrinthine dysfunction	MCL279	Neoplastic - Peritoneal carcinoma
MCL240	Labyrinthitis	MCL280	Neoplastic - Prostate Cancer
MCL241	Laryngitis	MCL281	Neoplastic - Renal cell carcinoma
MCL242	Lower respiratory tract inflammation	MCL282	Neoplastic - Retroperitoneal carcinoma
MCL243	Mastoiditis	MCL283	Neoplastic - Skin Cancer
MCL244	Meniere's disease	MCL284	Neoplastic - Stomach carcinoma
MCL245	Meningitis	MCL285	Neoplastic - Testicular carcinoma
MCL246	Menopause	MCL286	Neoplastic - Uterine carcinoma
MCL247	Metabolic - Dehydration/ metabolic derangement	MCL287	Neoplastic - Uterine tumor
MCL248	Metabolic - Diabetes Mellitus (new onset)	MCL288	Neoplastic - Vulvar carcinoma
MCL249	Middle ear adhesions	MCL289	Nephrolithiasis
MCL250	Mittelschmerz	MCL290	Neurological Condition - Inflammatory myelitis
MCL251	Mouth ulcer	MCL291	Neurological Condition - Bell's Palsy
MCL252	Multiple sclerosis	MCL292	Neuropathy - central, impingement related
MCL253	Myelodysplastic syndrome	MCL293	Non-fracture related acute compartment syndrome
MCL254	Myelofibrosis	MCL294	Non-specific abdominal pain
MCL255	Myocarditis	MCL295	Non-specific chest pain
MCL256	Myositis	MCL296	Non-specific eye pain
MCL257	Necrotizing fasciitis	MCL297	Non-specific headache
MCL258	Neoplastic - Adrenal neoplasm	MCL298	Non-specific musculoskeletal pain
MCL259	Neoplastic - Bladder carcinoma	MCL299	Non-specific peripheral neuropathy
MCL260	Neoplastic - Brain carcinoma	MCL300	Non-specific toothache/dental pain
MCL261	Neoplastic - Breast Cancer	MCL301	Orchitis
MCL262	Neoplastic - Carcinoid tumor	MCL302	Osteoarthritis
MCL263	Neoplastic - cervical carcinoma	MCL303	Osteoporosis
MCL264	Neoplastic – Chronic Lymphocytic Leukemia	MCL304	Other extremity trauma - high pressure injection injury
MCL265	Neoplastic – Chronic Myeloid Leukemia	MCL305	Other Lower extremity - Achilles' tendon injury
MCL266	Neoplastic - Colorectal Cancer	MCL306	Other Lower extremity - ankle dislocation / fracture
MCL267	Neoplastic - Esophageal carcinoma	MCL307	Other Lower extremity - Calcaneal bursitis
MCL268	Neoplastic - Fallopian tube neoplasm	MCL308	Other Lower extremity - Calcaneus / talus fracture
MCL269	Neoplastic - Hodgkin's disease	MCL309	Other Lower extremity - Lisfranc injury
MCL270	Neoplastic - Intestinal carcinoma	MCL310	Other Lower extremity - Medial gastrocnemius muscle strain

MCL311	Other Lower extremity - Peroneal tendon subluxation/ dislocation	MCL351	Respiratory Illness - Pneumonitis (inhalation injury)
MCL312	Other Lower extremity - Tibial shaft fracture	MCL352	Respiratory Illness - Acute Respiratory Distress Syndrome
MCL313	Other Lower extremity - Toe fracture	MCL353	Respiratory tract infection - lower
MCL314	Other Lower extremity -Plantar fasciitis	MCL354	Respiratory tract infection - upper
MCL315	Other Lower extremity -Proximal fibula fracture	MCL355	Retinal vascular occlusion
MCL316	Other Lower extremity -Stress fracture	MCL356	Rhabdomyolysis
MCL317	Otitis externa	MCL357	Rheumatoid arthritis
MCL318	Otitis media	MCL358	Sacral/coccygeal fracture
MCL319	Otosclerosis	MCL359	Sacroiliitis
MCL320	Ovarian cyst	MCL360	Salpingitis
MCL321	Ovarian failure	MCL361	Sarcoidosis
MCL322	Pain related to nerve root impingement/disc herniation	MCL362	Scapular fracture
MCL323	Palliative Treatment	MCL363	Schizophrenia
MCL324	Pancreatitis, acute	MCL364	Scleritis
MCL325	Panniculitis	MCL365	Scleroderma
MCL326	Parkinson's disease	MCL366	Sebaceous cyst
MCL327	Pemphigoid	MCL367	Seizures
MCL328	Pemphigus	MCL368	Sepsis
MCL329	Perforated tympanic membrane	MCL369	Septic arthritis
MCL330	Pericarditis	MCL370	Severe extremity injury
MCL331	Perichondritis	MCL371	Shock - cardiogenic
MCL332	Periodic paralysis	MCL372	Shock - neurogenic
MCL333	Periostitis	MCL373	Shoulder - Brachial plexus injury
MCL334	Phlebitis/Thrombophlebitis	MCL374	Shoulder - Clavicular fracture
MCL335	Pityriasis	MCL375	Shoulder - Humeral shaft fracture
MCL336	Polymyalgia rheumatica	MCL376	Shoulder - Proximal humerus fracture
MCL337	Post-phlebitis syndrome	MCL377	Sicca syndrome
MCL338	Pregnancy	MCL378	Skin abrasion
MCL339	Presbyopia	MCL379	Skin contusion/hematoma
MCL340	Prostatitis, acute	MCL380	Skin infection - viral/fungal
MCL341	Psoriasis	MCL381	Skin laceration
MCL342	Pterygium	MCL382	Systemic Lupus Erythematous
MCL343	Pulmonary barotrauma	MCL383	Small bowel obstruction
MCL344	Pulmonary hypertension	MCL384	Space adaptation - back pain
MCL345	Pyelonephritis	MCL385	Space adaptation - constipation
MCL346	Radiation Induced Coagulopathy (RIC)	MCL386	Space adaptation - epistaxis
MCL347	Rash, spaceflight associated	MCL387	Space adaptation - headache
MCL348	Reactive airway/asthma	MCL388	Space adaptation - insomnia
MCL349	Renal sclerosis	MCL389	Space adaptation - nasal congestion
MCL350	Respiratory failure	MCL390	Space adaptation - space motion sickness

MCL391	Space adaptation - urinary retention	MCL421	Transient global amnesia
MCL392	Space adaptation - urinary incontinence	MCL422	Transient ischemic attack
MCL393	Spaceflight associated neuro-ocular syndrome (sans)	MCL423	Trauma - abdominal injury (blunt)
MCL394	Spermatocele	MCL424	Trauma - abdominal injury (penetrating)
MCL395	Spinal cord injury	MCL425	Trauma - chest injury (blunt)
MCL396	Sprain/strain - back	MCL426	Trauma - chest injury (penetrating)
MCL397	Sprain/strain - lower extremity	MCL427	Trauma - minor head
MCL398	Sprain/strain - neck	MCL428	Trauma - severe head
MCL399	Sprain/strain - upper extremity	MCL429	Trauma - spinal cord injury (sci), cervical
MCL400	Streptococcal pharyngitis	MCL430	Trauma - spinal cord injury (sci), thoracic/lumbar
MCL401	Sub-corneal pustular dermatosis	MCL431	Traumatic hypovolemic shock
MCL402	Sudden cardiac arrest	MCL432	Trigeminal neuralgia
MCL403	Suicidality	MCL433	Tympanosclerosis
MCL404	Supraventricular tachycardia	MCL434	Urinary incontinence (non-space adaptation)
MCL405	Synovial/bursal cyst	MCL435	Urinary tract infection
MCL406	Systemic sclerosis	MCL436	Ultraviolet Keratitis
MCL407	Takotsubo syndrome	MCL437	Uveitis
MCL408	Tendinopathy/enthesopathy/bursitis/over-use injuries - lower extremity	MCL438	Vaginal yeast infection
MCL409	Tendinopathy/enthesopathy/bursitis/over-use injuries - upper extremity	MCL439	Vascular myelopathies
MCL410	Testicular failure	MCL440	Venous thromboembolism
MCL411	Thromboangiitis obliterans	MCL441	Venous Thromboembolism - thrombus in situ
MCL412	Thyroid neoplasm	MCL442	Vertebral disc disorder
MCL413	Thyroiditis	MCL443	Vestibular neuronitis
MCL414	Tinnitus	MCL444	Vitamin B deficiency
MCL415	Torticollis	MCL445	Vitamin D deficiency
MCL416	Toxic atmosphere - Other environmental ingestion exposures (ex: trialkylamines, water contamination, microbes)	MCL446	Vitreous Detachment
MCL417	Toxic atmosphere - Other environmental inhalation exposures (ethylene glycol)	MCL447	Volvulus
MCL418	Toxic dermal exposure	MCL448	Wegner's granulomatosis
MCL419	Toxic inhalation exposure	MCL449	Wrist dislocation
MCL420	Toxic inhalation exposure - combustion products	MCL450	Wrist Sprain/Strain

APPENDIX E PROPOSED FUTURE CONDITIONS LIST (PFCL)

PFCL1	BHP - Delirium	PFCL47	Necrotizing fasciitis
PFCL2	Breast lump/mass	PFCL48	Neoplastic - Adrenal neoplasm
PFCL3	Cardiac conduction abnormalities	PFCL49	Neoplastic - Bladder carcinoma
PFCL4	Chest Wall Inflammation/ Costochondritis	PFCL50	Neoplastic - Brain carcinoma
PFCL5	Cholangitis	PFCL51	Neoplastic - Breast Cancer
PFCL6	Chronic Diarrhea	PFCL52	Neoplastic - Carcinoid tumor
PFCL7	Dental caries	PFCL53	Neoplastic – Cervical Carcinoma
PFCL8	Dislocation – Elbow	PFCL54	Neoplastic – Chronic Lymphocytic Leukemia
PFCL9	Dislocation - Hip / Pelvis	PFCL55	Neoplastic – Chronic Myeloid Leukemia
PFCL10	Dislocation - Patella	PFCL56	Neoplastic - Colorectal Cancer
PFCL11	Dislocation/Fracture - Foot/ankle	PFCL57	Neoplastic - Esophageal carcinoma
PFCL12	Dust exposure - Martian	PFCL58	Neoplastic - Fallopian tube neoplasm
PFCL13	Dysbaric Osteonecrosis	PFCL59	Neoplastic – Hodgkin’s Disease
PFCL14	Electrical Injury	PFCL60	Neoplastic - Intestinal carcinoma
PFCL15	EVA Eye Irritation	PFCL61	Neoplastic – Liver carcinoma
PFCL16	EVA Related Lower Extremity Sprain/Strain	PFCL62	Neoplastic - Lung carcinoma
PFCL17	EVA Related Skin Hematoma/Contusion	PFCL63	Neoplastic - Multiple myeloma
PFCL18	EVA Related Suit Failure	PFCL64	Neoplastic – Non-Hodgkin's lymphoma
PFCL19	EVA related upper extremity strain/sprain	PFCL65	Neoplastic - Oropharyngeal carcinoma
PFCL20	Eye trauma / injury - Orbital Wall Fracture	PFCL66	Neoplastic - Ovarian carcinoma
PFCL21	Facial trauma - mandibular dislocation	PFCL67	Neoplastic - Pancreatic carcinoma
PFCL22	Facial trauma - mandibular fracture	PFCL68	Neoplastic - Penile carcinoma
PFCL23	Facial trauma - maxillary fracture	PFCL69	Neoplastic - Peritoneal carcinoma
PFCL24	Facial trauma - nasal bone fracture	PFCL70	Neoplastic - Prostate Cancer
PFCL25	Facial trauma - septal hematoma	PFCL71	Neoplastic - Renal cell carcinoma
PFCL26	Facial trauma - zygomatic fracture	PFCL72	Neoplastic - Retroperitoneal carcinoma
PFCL27	Fingernail Hematoma	PFCL73	Neoplastic - Skin Cancer
PFCL28	Fracture - compression, thoracic/lumbar spine	PFCL74	Neoplastic - Stomach carcinoma
PFCL29	Fracture - pelvis	PFCL75	Neoplastic - Testicular carcinoma
PFCL30	Fracture - shoulder	PFCL76	Neoplastic - Uterine carcinoma
PFCL31	Gastrointestinal considerations - Diverticulosis	PFCL77	Neoplastic - Uterine tumor
PFCL32	Genital Concerns - Bacterial vaginosis	PFCL78	Neoplastic - Vulvar carcinoma
PFCL33	Genital Concerns - Pregnancy - Ectopic	PFCL79	Neurological Condition - Bell's Palsy
PFCL34	Genital Concerns - Pregnancy - Incomplete abortion	PFCL80	Non-fracture related acute compartment syndrome
PFCL35	Genital Concerns - Pregnancy - Intrauterine	PFCL81	Orchitis
PFCL36	Genital Concerns - Pregnancy - Missed abortion	PFCL82	Ovarian cyst
PFCL37	Genital Concerns - Pregnancy - Retained products of conception	PFCL83	Perforated tympanic membrane
PFCL38	Genital Concerns - Pregnancy - Spontaneous abortion	PFCL84	Phlebitis/Thrombophlebitis
PFCL39	Genital Concerns - Pregnancy - Threatened abortion	PFCL85	Pulmonary barotrauma

PFCL40	Glaucoma/ocular Hypertension	PFCL86	Septic arthritis
PFCL41	Hyperlipidemia	PFCL87	Shock - neurogenic
PFCL42	Hypertension	PFCL88	Toxic atmosphere - Other environmental ingestion exposures (ex: trialkylamines, water, microbes)
PFCL43	Impingement syndromes - peripheral	PFCL89	Trauma - abdominal injury (penetrating)
PFCL44	Iron deficiency	PFCL90	Trauma - chest injury (penetrating)
PFCL45	Knee - Pes anserine, prepatellar bursitis	PFCL91	Trauma - spinal cord injury (sci), cervical
PFCL46	Metabolic - Diabetes Mellitus (new onset)	PFCL92	Trauma - spinal cord injury (sci), thoracic/lumbar

APPENDIX F REMOVED CONDITIONS LIST (RCL)

ID	CONDITION	Existing Condition Which Encompasses the Removed Condition
RCL1	Adjustment disorder	ICL13 - BHP - Adjustment Disorder
RCL2	Allergic rhinitis	ICL82 - Respiratory Tract Infection - Upper
RCL3	Angina/myocardial infarction	ICL3 - Acute Coronary Syndrome
RCL4	Behavioral emergency	ICL17 - BHP - Psychosis Secondary to Depression
RCL5	Chemical burn	ICL19 - Burn - Chemical Eye ICL20 - Burn - Chemical Skin
RCL6	Cracked tooth	ICL31 - Dental Fracture/Exposed Pulp
RCL7	Delirium	PFCL1 - Bhp - Delirium
RCL8	Elbow - epicondylitis	ICL108 - Tendinopathy/Enthesopathy/Bursitis/Over-Use Injuries - Upper Extremity
RCL9	Elbow -radial head / supracondylar / olecranon fracture	ICL51 - Fracture - Arm
RCL10	Elbow sprain/strain	ICL104 - Sprain/Strain - Upper Extremity¥
RCL11	Enthesopathy	ICL107 - Tendinopathy/Enthesopathy/Bursitis/Over-Use Injuries - Lower Extremity ICL108 - Tendinopathy/Enthesopathy/Bursitis/Over-Use Injuries - Upper Extremity
RCL12	EVA (surface) related friction injury	ICL46 - Eva Related Suit Contact Injury
RCL13	Extreme pain of unclear etiology*	
RCL14	Eye irritation/abrasion	ICL49 - Eye Irritation/Corneal Abrasion/Ulceration
RCL15	Eye trauma / injury - Retinal Burn	ICL47 - Eye - Retinal Injury
RCL16	Eye trauma / injury - Retinal Tear	ICL47 - Eye - Retinal Injury
RCL17	Finger - finger tendon injury	ICL104 - Sprain/Strain - Upper Extremity¥
RCL18	Foot fracture/dislocation	PFCL11 - Dislocation/Fracture - Foot/Ankle†
RCL19	Foot sprain	ICL102 - Sprain/Strain - Lower Extremity§
RCL20	Foot/ankle sprain/strain	ICL102 - Sprain/Strain - Lower Extremity§
RCL21	Gastroenteritis	ICL59 - Gastroenteritis/Acute Diarrhea
RCL22	Gastrointestinal considerations - Peptic Ulcer Disease	ICL58 - Gastritis/Reflux/Esophagitis
RCL23	Genital Concerns - Ovarian cysts - ruptured	PFCL82 - Ovarian Cyst°
RCL24	Genital Concerns - Ovarian cysts -hemorrhagic	PFCL82 - Ovarian Cyst°
RCL25	Hip / Pelvis - Lateral femoral cutaneous nerve entrapment	ICL72 - Neuropathy - Central, Impingement Related
RCL26	Hip / Pelvis - Sciatica/piriform syndrome	ICL72 - Neuropathy - Central, Impingement Related
RCL27	Hip / Pelvis - Trochanteric / iliopectineal/iliopsoas bursitis	ICL107 - Tendinopathy/Enthesopathy/Bursitis/Over-Use Injuries - Lower Extremity ICL108 - Tendinopathy/Enthesopathy/Bursitis/Over-Use Injuries - Upper Extremity
RCL28	Humeral Fracture	ICL51 - Fracture - Arm
RCL29	Influenza	ICL 81 - Respiratory Tract Infection - Lower
RCL30	Iron deficiency anemia	PFCL44 - Iron Deficiency
RCL31	Knee - Knee fracture	ICL53 - Fracture - Distal Leg
RCL32	Knee sprain/strain	ICL102 - Sprain/Strain - Lower Extremity§

RCL33	Lower respiratory tract inflammation	ICL36 - Dust Exposure - Lunar ICL79 - Reactive Airway ICL81 - Respiratory Tract Infection - Lower ICL110 - Toxic Inhalation Exposure
RCL34	Non-specific abdominal pain*	
RCL35	Non-specific chest pain*	
RCL36	Non-specific eye pain*	
RCL37	Non-specific headache*	
RCL38	Non-specific musculoskeletal pain*	
RCL39	Non-specific peripheral neuropathy*	
RCL40	Non-specific toothache/dental pain*	
RCL41	Osteoarthritis	ICL9 - Arthritis, Acute
RCL42	Other Lower extremity - Achilles' tendon injury	ICL102 - Sprain/Strain - Lower Extremity§
RCL43	Other Lower extremity - ankle dislocation / fracture	PFCL11 - dislocation/fracture - Foot/Ankle†
RCL44	Other Lower extremity - Calcaneus / talus fracture	PFCL11 - dislocation/fracture - Foot/Ankle†
RCL45	Other Lower extremity - Lisfranc injury	PFCL11 - dislocation/fracture - Foot/Ankle†
RCL46	Other Lower extremity - Medial gastrocnemius muscle strain	ICL102 - Sprain/Strain - Lower Extremity§
RCL47	Other Lower extremity - Tibial shaft fracture	ICL53 - Fracture - Distal Leg
RCL48	Other Lower extremity - Toe fracture	PFCL11 - dislocation/fracture - Foot/Ankle†
RCL49	Other Lower extremity -Proximal fibula fracture	ICL53 - Fracture - Distal Leg
RCL50	Other Lower extremity -Stress fracture	ICL53 - Fracture - Distal Leg
RCL51	Pain related to nerve root impingement/disc herniation	ICL72 - Neuropathy - Central, Impingement Related
RCL52	Pyelonephritis	ICL117 - Urinary Tract Infection
RCL53	Respiratory Illness - Pneumonitis (inhalation injury)	ICL36 - Dust Exposure - Lunar ICL110 - Toxic Inhalation Exposure
RCL54	Respiratory Illness - Acute Respiratory Distress Syndrome	ICL80 - Respiratory Failure
RCL55	Scapular fracture	PFCL30 - Fracture - Shoulder
RCL56	Severe extremity injury*	
RCL57	Shoulder - Brachial plexus injury	ICL72 - Neuropathy - Central, Impingement Related
RCL58	Shoulder - Clavicular fracture	PFCL30 - Fracture – Shoulder
RCL59	Shoulder - Humeral shaft fracture	ICL51 - Fracture - Arm
RCL60	Shoulder - Proximal humerus fracture	ICL51 - Fracture - Arm
RCL61	Spinal cord injury	PFCL91 - Trauma - Spinal Cord Injury (Sci), Cervical PFCL92 - Trauma - Spinal Cord Injury (Sci), Thoracic/Lumbar
RCL62	Suicidality	ICL15 - Bhp - Depression
RCL63	Toxic atmosphere - Other environmental inhalation exposures (ethylene glycol)	ICL110 - Toxic Inhalation Exposure

RCL64	Transient ischemic attack	ICL23 - Cerebrovascular Accident
RCL65	Venous Thromboembolism - thrombus in situ	ICL119 - Venous Thromboembolism
RCL66	Wrist sprain/strain	ICL104 - Sprain/Strain - Upper Extremity¥

*Denotes a condition that was too vague, limiting the ability to diagnose, obtain incidence data, assign medical resources, and assign associated task impairment values.
ŧ"PFCL11 - dislocation/fracture - Foot/ankle" has the following CNES: Foot fracture/dislocation, Ankle fracture/dislocation, Calcaneus fracture/Talus Fracture, Lisfranc Injury, and Toe Fracture
¥All upper extremity sprains/strains were combined to form this condition.
§All lower extremity sprains/strains were combined to form this condition.
°Ovarian cyst, hemorrhagic ovarian cyst, and ruptured ovarian cyst were combined to form this condition.

APPENDIX G ALL REMAINING CONDITIONS LIST (ARCL)

ID	CONDITION	ID	CONDITION
ARCL1	Acquired ovarian atrophy	ARCL35	Corneal vascularization
ARCL 2	Acute Anemia - hypovolemic	ARCL36	Coronary artery aneurysm
ARCL3	Acute neuropraxia (e.g., stretched nerve)	ARCL37	Coronary artery dissection
ARCL4	Acute tubular necrosis	ARCL38	Dermatological - Pressure injury
ARCL5	Adhesive capsulitis	ARCL39	Dermatological - Soft tissue foreign body
ARCL6	Amyotrophic Lateral Sclerosis	ARCL40	Dermatomyositis
ARCL7	Amyloidosis	ARCL41	Diabetes insipidus
ARCL8	Anal fissure	ARCL42	Disseminated Intravascular Coagulopathy (DIC)
ARCL9	Anal rectal/polyp	ARCL43	Dissociative disorder
ARCL10	Aortic aneurysm	ARCL44	Dysmenorrhea
ARCL11	Aortic Dissection	ARCL45	Ectopic beats (Premature Ventricular/Atrial Contractions)
ARCL12	Aortic ectasia	ARCL46	Endocarditis
ARCL13	Artery stricture	ARCL47	Endocrine - hyperthyroidism
ARCL14	Aseptic necrosis	ARCL48	Endocrine - hypothyroidism
ARCL15	Autonomic dysreflexia	ARCL49	Endocrine - Parathyroidism
ARCL16	Bartholin's gland abscess	ARCL50	Endocrine - Pituitary adenoma
ARCL17	Benign neoplasm	ARCL51	Endomyocardial fibrosis
ARCL18	Biliary cirrhosis	ARCL52	Entropion
ARCL19	Bipolar disorder	ARCL53	Epididymitis
ARCL20	Blepharitis	ARCL54	Erythema multiforme
ARCL21	Benign Paroxysmal Positional Vertigo	ARCL55	Erythema nodosum
ARCL22	Bullous dermatosis	ARCL56	Esophageal Spasm/Inflammation
ARCL23	Calculus of prostate	ARCL57	Esophageal stricture
ARCL24	Cataract	ARCL58	Essential thrombocytopenia
ARCL25	Celiac disease	ARCL59	Eye - retained foreign Body
ARCL26	Cellulitis, Periorbital	ARCL60	Eye trauma / injury - Eyelid laceration
ARCL27	Central sleep apnea	ARCL61	Eye trauma / injury - Orbital cellulitis
ARCL28	Chalazion	ARCL62	Fasciitis
ARCL29	Chondromalacia patellae	ARCL63	Felon (digit)
ARCL30	Chorioretinitis	ARCL64	Furunculitis
ARCL31	Choroidal detachment	ARCL65	Gastrointestinal considerations - Gastrointestinal bleed
ARCL32	Complex Regional Pain	ARCL66	Gastrointestinal considerations - Ischemic colitis
ARCL33	Constipation (non-SA)	ARCL67	Gastrointestinal considerations - Ulcerative Colitis
ARCL34	Corneal dystrophy	ARCL68	Gastrointestinal considerations -Clostridium Difficile

ARCL69	Genital Concerns - Endometriosis	ARCL104	Meniere's disease
ARCL70	Genital Concerns - Epididymitis	ARCL105	Meningitis
ARCL71	Genital Concerns - Ovarian torsion	ARCL106	Menopause
ARCL72	Genital Concerns - Paraphimosis	ARCL107	Metabolic - Dehydration/ metabolic derangement
ARCL73	Genital Concerns - Sexually Transmitted infection	ARCL108	Middle ear adhesions
ARCL74	Genital Concerns - Testicular torsion	ARCL109	Mittelschmerz
ARCL75	Genital Concerns – Tubo-ovarian Abscess	ARCL110	Musculoskeletal back pain (non-Space Adaptation)
ARCL76	Genital Concerns - Phimosis	ARCL111	Multiple sclerosis
ARCL77	Genital Concerns - Priapism	ARCL112	Myelodysplastic syndrome
ARCL78	Giant cell arteritis	ARCL113	Myelofibrosis
ARCL79	Gingivitis/periodontitis	ARCL114	Myocarditis
ARCL80	Glomerulonephritis	ARCL115	Myositis
ARCL81	Hemolytic anemia	ARCL116	Neurological Condition - Inflammatory myelitis
ARCL82	Hidradenitis	ARCL117	Osteoporosis
ARCL83	Hip / Pelvis - Gluteal Medius tears	ARCL118	Other extremity trauma - high pressure injection injury
ARCL84	Hip / Pelvis - Osteitis pubis	ARCL119	Other Lower extremity - Calcaneal bursitis
ARCL85	Hip / Pelvis - Snapping hip	ARCL120	Other Lower extremity - Peroneal tendon subluxation / dislocation
ARCL86	Histiocytosis	ARCL121	Other Lower extremity -Plantar fasciitis
ARCL87	Hypersensitivity angiitis	ARCL122	Otosclerosis
ARCL88	Hypoxia	ARCL123	Ovarian failure
ARCL89	IBS	ARCL124	Palliative Treatment
ARCL90	Inflammatory disease of breast	ARCL125	Panniculitis
ARCL91	Ingrown Toenail	ARCL126	Parkinson's disease
ARCL92	Inguinal/femoral hernia (Advanced Resistive Exercise Device-induced)	ARCL127	Paronychia
ARCL93	Interstitial lung disease	ARCL128	Pemphigoid
ARCL94	Intussusception	ARCL129	Pemphigus
ARCL95	Iridocyclitis	ARCL130	Pericarditis
ARCL96	Idiopathic Thrombocytopenia Purpura	ARCL131	Perichondritis
ARCL97	Joint ankylosis/ankylosis spondylitis	ARCL132	Periodic paralysis
ARCL98	Kidney / Urinary - obstructive / Benign Prostatic hyperplasia	ARCL133	Periostitis
ARCL99	Labyrinthine dysfunction	ARCL134	Pityriasis
ARCL100	Labyrinthitis	ARCL135	Polymyalgia rheumatica
ARCL101	Laryngitis	ARCL136	Post-phlebitis syndrome
ARCL102	Mastitis	ARCL137	Presbyopia
ARCL103	Mastoiditis	ARCL138	Psoriasis

ARCL139	Pterygium	ARCL162	Synovial/bursal cyst
ARCL140	Pulmonary hypertension	ARCL163	Systemic sclerosis
ARCL141	Radiation Induced Coagulopathy (RIC)	ARCL164	Takotsubo syndrome
ARCL142	Renal sclerosis	ARCL165	Testicular failure
ARCL143	Retinal vascular occlusion	ARCL166	Thromboangiitis obliterans
ARCL144	Rhabdomyolysis	ARCL167	Thyroid neoplasm
ARCL145	Rheumatoid arthritis	ARCL168	Thyroiditis
ARCL146	Sacral/coccygeal fracture	ARCL169	Tinnitus
ARCL147	Sacroiliitis	ARCL170	Torticollis
ARCL148	Salpingitis	ARCL171	Transient global amnesia
ARCL149	Sarcoidosis	ARCL172	Trigeminal neuralgia
ARCL150	Schizophrenia	ARCL173	Tympanosclerosis
ARCL151	Scleritis	ARCL174	Urinary incontinence (non-spaceflight adaptation)
ARCL152	Scleroderma	ARCL175	Ultraviolet Keratitis
ARCL153	Sebaceous cyst	ARCL176	Uveitis
ARCL154	Seborrheic Dermatitis	ARCL177	Vascular myelopathies
ARCL155	Sicca syndrome	ARCL178	Vestibular neuronitis
ARCL156	Skin contusion/hematoma	ARCL179	Vitamin B deficiency
ARCL157	Systemic Lupus Erythematous	ARCL180	Vitamin D deficiency
ARCL158	Spermatocele	ARCL181	Vitreous Detachment
ARCL159	Sub-corneal pustular dermatosis	ARCL182	Volvulus
ARCL160	Subcutaneous Abscess	ARCL183	Wegner's granulomatosis
ARCL161	Supraventricular tachycardia	ARCL184	Wrist dislocation

APPENDIX H ACRONYMS AND ABBREVIATIONS

Acronym/Abbreviation	Definition
AAOMS	American Association of Oral and Maxillofacial Surgeons
ADLs	Activities of Daily Living
AMA	American Medical Association
ARCL	All Remaining Conditions List
ARS	Acute Radiation Syndrome
BC	Best-case
BHP	Behavioral Health and Performance
CAC	Coronary Artery Calcium
CHS	Crew Health & Safety
CL	Condition list
CLiFF	Clinical Finding Form
CMO	Crew Medical Officer
CNES	Conditions Not Explicitly Stated [but included in the ICL 1.0]
ConOps	Concept of operations
CP	Clinical Phase
CP1	Clinical Phase 1
CP2	Clinical Phase 2
CP3	Clinical Phase 3
CRT	Capability Resource Table
CTI	Crew Task Index
CTT	Condition Task Total
CUSOM	University of Colorado School of Medicine
DCS	Decompression Sickness
DRM	Design Reference Mission
DTIC	Defense Technical Information Center
EBM	Evidence based medicine
EL	Evidence Library
EMCL	Exploration Medical Condition List
Env	Environmental Exposures
EVA	Extravehicular activity
ExMC	Exploration Medical Capability Element
ExMCCB	Exploration Medical Capability Element Control Board
FI	Functional Impairment
FoM	Figures of Merit
GRC	Glenn Research Center
GWT	Gravity Well Transition
HRP	Human Research Program
HSTC	Human System Task Category
ICD	International Classification of Disease
ICL 1.0	IMPACT 1.0 Medical Conditions List

IM	Intramuscular
IMCL	IMM Medical Condition List
iMED	Integrated Medical Evidence Database
IMM	Integrated Medical Model
IMPACT	Informing Mission Planning via Analysis of Complex Tradespaces
IMPACT-MD	IMPACT Medical Database
IP	Incidence Proportion
IR	Incidence Rate
ISS	International Space Station
IV	intravenous
JSC	Johnson Space Center
KSAs	Knowledge Skills and Abilities
LD	Medical Database Lockdown
LEO	low-Earth orbit
LEVA	Lunar Extravehicular Activities
LOC	Level of Confidence
LOCL	Loss of Crew Life
LOM	Loss of Mission
LSAH	Lifetime Surveillance of Astronaut Health
LSO	Lunar Surface Operations
MCL	Master Condition List
MEDPRAT	Medical Extensible Dynamic Probabilistic Risk Assessment Tool
MeSH	Medical Subject Headings
MEVA	Martian Extravehicular Activities
MSO	Martian Surface Operations
MTL	Mars Task List
N/A	Not applicable
NASA	National Aeronautics and Space Administration
NTRS	NASA Technical Reports Server
OBGYN	Obstetrics and Gynecology
PDR	Preliminary Design Review
PFCL	Proposed Future Conditions List
PO	Per os (taken by mouth)
PRA	Probabilistic Risk Assessment
PTRS	Project Technical Requirements Specification
QTL	Quality Time Lost
RCL	Removed Conditions List
REP	Rochester Epidemiology Project
RTDC	Removal to definitive care
RTDC	Removal to definitive care
SANS	Spaceflight-Associated Neuro-ocular Syndrome
SAS	Space Adaptation Syndrome
SBR	System requirements overview
SD	Standard deviation

SEVA	Space Extravehicular Activities
SME	Subject matter expert
SME	Subject matter expert
SoP	Scope of Practice code
SPE	Solar particle event
SRR	Systems Requirements Review
TI	Task Impairment
TMT	Total Mission Tasks
TTL	Task Time Lost
US	United States
V&V	Verification and Validation
VIIP	Visual Impairment/Intracranial Pressure
WC	Worst-case
WinBUGS	Windows Bayesian inference Using Gibbs Sampling

APPENDIX I CLiFF PEER REVIEW FORM

CLiFF PEER Review

1. *Strength of evidence presented in CLiFF in modeling the characteristics and mission impact of this medical condition within the spaceflight environment.*

   Score:

   Grading Scale:
   4 - Confident
   3 - Somewhat confident
   2 – Neutral
   1 – Somewhat unconfident
   0 – Not confident

2. How confident are you that these data accurately represent the spaceflight environment?	*Tables 1, 2 Composite Incidence and Level of Confidence*	*Table 3, 4 BC/WC LOC and probability*	*Table 4 - Clinical Phase 1, 2 durations Table 5 – CP 2 LOC*	*Table 4 – RTDC % Table 6 – RTDC LOC*	*Table 4 – LOCL % Table 7 – LOCL LOC*	*Table 8 – TI*
Score						

Comments and limitations:

1. **General comments:**
2. **Incidence:**
3. **Clinical phase data**:
4. **Task Impairment**:
5. **Dependence on mission phase or duration of mission**:
6. **Limitations:**

Reviewed by: