Clinical Finding Form (CliFF)

Branch Baseline

ICL100_Space Flight Associated Neuro-Ocular Syndrome (Sans)

For the last several decades it has been known that there are changes in visual acuity among astronauts that are due to a complex combination of retinal, ocular, and neurological changes during spaceflight. Several theories to the underlying etiology exist including cephalad fluid shifts, venous congestion, ischemia and inflammation but none seem to completely explain the observed changes. Crew members have been found to have hyperopic shifts, choroidal folds, kinks in the optic nerve, flattening of the posterior globe, increased ICP and several other abnormal findings that are not consistent with terrestrial ophthalmologic diseases. Initially this condition was called Visual Impairment with Increased Intracranial Pressure (VIIP) but more recently has been renamed Spaceflight Associated Neuro-ocular Syndrome (SANS). This constellation of changes has been hard to characterize and classify into a clear and distinct disease process as there is substantial variability among crew members. More recently there has been standardization with the use of ocular coherence tomography among all crew members preflight, in-flight, and post flight which shows total retinal thickness (TRT) changes as one of the most reliable and consistent pathophysiologic findings. The onset of this process can start within 14 day and the end point of these changes is still unclear but the incidence of this condition is much higher in long duration flight than short duration which is troubling for lunar and mars mission planning. For crew members with visual acuity changes due to hyperopic shift, "space anticipation glasses" have been used effectively. Other countermeasures to changes in IOP or ICP are still theoretical and have unclear clinical benefit. Much is still unknown about this disease and in preparing this CLIFF the definition and criteria for SANS was being updated based on new data. Our understanding and mitigation of these visual and neurologic changes is expected to evolve substantially in the ensuing years.

INCIDENCE DATA INCLUDED IN THE 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

Spaceflight incidence data is taken from the LSAH which monitors astronaut health prior to , during, and after flight. Deidentified confidential data was used to determine the incidence. This condition is unique to spaceflight and only being monitored by NASA clinicians and researchers. Astronaut health record information is protected and due to the limited number of astronauts each year, much of the LSAH data is limited and unpublished.

ANALOG LITERATURE

There have been several "head down" analog studies performed in an attempt to replicate the pathophysiology of SANS but they have had varied results and are much less accurate than spaceflight data. These studies involve placing patients in a supine or prone position for weeks or months at a time and measuring retinal thickness, visual acuity and retinal architectural changes.

TERRESTRIAL LITERATURE

No terrestrial literature for this condition exists

OVERALL INCIDENCE SUMMARY

INCIDENCE

Mean 0.2789 and SD 0.08342

INCIDENCE SUMMARY

The Bayesian posterior distribution for the incidence proportion given the spaceflight evidence (7 cases out of 27 unique astronaut missions that had full testing), under an uninformative prior is Beta(alpha=7.781, beta=20.119) with mean 0.2789 and SD 0.08342. Data set includes a minimum mission duration of 60 days and a maximum of 120 days. Crew members with abnormal findings but incomplete data were excluded from this calculation. This includes shuttle astronauts which implies a onset of disease within 14 days as this was a common mission duration. Probability of worst case is 0.14 (1/7) amongst all cases (detected on any test). Data is entirely based on microgravity environment and the role of partial gravity on the development of this condition is unknown. SANS will be modeled as a "Yes or No" condition meaning once a crew member has the condition they will continue to have the condition through the remainder of the flight. This is different than most conditions with regards to IMPACT modeling. Each crew member will be modeled individually. Changes are defined as OCT testing in flight showing abnormalities when compared to L-9/6 mo. Spaceflight definition of a case includes any of the following •>55-micron change in total retinal thickness in at least one eye •Choroidal folds anywhere in at least one eye •Visual acuity change in at least one eye >=0.75 diopters – only measured pre- and post-flight. Total cases/over total tested (at least 1 test) = 10/34 person-missions (including some repeat fliers)…. (Of those that had all 3 measures – change in total retinal thickness, change in visual acuity, and folds assessment – 8/28 with one repeat or 7/27 for unique astronauts). After talking over the testing, we decided to use the set of full testing with only unique fliers – 7 cases over 27 person-missions). IP: 0.2593 (95%CI: 0.1111, 0.4628)

TABLE 1. INCIDENCE MODEL

Incidence Details

Incidence Type
SAS

Segment
Space Adaptation

Env. Exposure
NA

Sex
Any

Crowns
Any

Contacts
Any

Pregnancy
Any

Incidence Distribution

Occurrence Dist
Binomial

Incidence Dist.
Beta

Mean
0.278889

SD
0.0834195

Beta
(Alpha): 7.781
(Beta): 20.119

Onset Timing (Hours)
(Min): 336
(Max): 2880
(Most Likely): 720

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
AOHMG data request - SANS estimates for IMPACT	Spaceflight	4

The LSAH data utilized for the incidence of SANS is the gold standard for calculating incidence as this is a condition unique to spaceflight and only captured by NASA physicians at this time. The data set has some incomplete measures and includes astronauts on multiple missions and had to be trimmed to maximize accuracy based on current definitions.

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 PREVENTATIVE MEASURES

There is a required preflight ophthalmologic examination among all crew members which includes extensive testing including visual fields, depth perception, retinal photography, OCT, tonometry and several other tests. Not all of these test are disqualifying if abnormal but do provide a very clear baseline among crew members. Ophthalmologic examinations also occur yearly or every 3 years (depending on the test) to monitor for changes over time.

BEST CASE SCENARIO DEFINITION

>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.

WORSE CASE SCENARIO DEFINITION

>200um change in total retinal thickness (TRT), choroidal folds overlying the fovea, or visual field defects with blind spots

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

Among the 7 unique crew members meeting criteria for SANS, 1 of them met the criteria for our WC definition. This astronaut had >200um TRT but did not meet the other criteria. Thus 1/7 or 14% was our WC probability

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

Citation	Source	LOC Value
AOHMG data request - SANS estimates for IMPACT	Spaceflight	4

The ExMC clinical science team and the SANS research group worked to develop best and worst case definitions for this spaceflight specific condition. The LSAH dataset was then used to determine the proportion of astronauts that met criteria for the BC and WC definitions to determine ratio. There are substantial limitations to this dataset but this is the best available data at this time.

TABLE 4. CLIFF TREATMENT & OUTCOME TABLE BY CLINICAL PHASE

Case Scenario	Composite 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 0.2789 and SD 0.08342	86 - 86	100	2.12	22.6947	0	12	0	0	0	0	0
Treated Worst Case (TWC)		14 - 14	100	2.12	49.4552	0	12	0	0	0	0	0
Untreated Best Case (UTBC)	N/A	N/A	N/A	2.12	31.8097	0	12	22.6947	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	2.12	49.4552	0	12	31.8097	0	0	0	0

TABLE 4 KEY

Composite Incidence: The same composite 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

SANS appears to start within the first 2 weeks of zero G exposure and persist until several months after return to the 1G environment. This is based on abnormal ocular findings among shuttle astronauts with mission durations of 14 days. These findings were early in our understanding of SANS and did not include consistent enough measurements to be included in our dataset but do allude to a rapid onset of disease. The effect of a partial G environment is still unclear. Typically a crew member will notice small visual changes or abnormalities on retinal screening images will show abnormalities. Those with visual acuity effects will improve with "space anticipation glasses". Other countermeasures for changes in ICP or IOP are theoretical at this point.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

The BC definition for this condition was >55um 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. The duration of this condition was determined based on expert opinion to be 0-12 hours. The RTDC and LOCL are 0% based on condition definition.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

The WC definition for this condition is >200um change in total retinal thickness (TRT), choroidal folds overlying the fovea, or visual field defects with blind spots. The duration for this condition was determined to be 0-12 hours based on expert opinion. RTDC and LOCL are both 0% based on condition definition.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

The BC definition for this condition was >55um 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. The duration of this condition was determined based on expert opinion to be 0-12 hours. The RTDC and LOCL are 0% based on condition definition.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

The WC definition for this condition is >200um change in total retinal thickness (TRT), choroidal folds overlying the fovea, or visual field defects with blind spots. The duration for this condition was determined to be 0-12 hours based on expert opinion. RTDC and LOCL are both 0% based on condition definition.

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

Citation	Source	LOC Value
Expert Opinion	Terrestrial	2

Duration of CP2 was determined to be 0-12 hours in all forms of this condition. This was based on subject matter expert opinion regarding estimated time of treatment. At this time there is not any treatment other than corrective glasses and thus this range was chosen to reflect the limited necessary interventions.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
NA	NA	4

RTDC surrogate defines RTDC as 0%

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
NA	NA	4

This condition has no risk of LOCL by definition. There have been no observed cases that have endangered a crew member

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope

Overview
SANS is an investigational condition that is not well understood. Diagnosis will largely follow what is currently done for research purposes on ISS and treatment is limited to refraction for vision correction. Since the mechanisms are not known, there are no preventive or curative measures available. To date, vision correction as symptom management is effective and sufficient for management. This is expected to be an active area of research on future flights so there will likely be additional resources allocated for management as more information is gained. However, none are included here due to their experimental nature and unknown efficacy.

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): 2.12 hours for set up, history, and a thorough ophthalmic exam involving fundoscopic, vision, OCT, and intraocular pressure testing. A focused neurological exam and ophthalmic ultrasound are also included.

CP1 WC (Treated or Untreated): 2.12 hours for set up, history, and a thorough ophthalmic exam involving fundoscopic, vision, OCT, and intraocular pressure testing. A focused neurological exam and ophthalmic ultrasound are also included. This is no different than the best case definition because the testing is expected to be the same.

This condition requires a Scope of Practice 5 largely due to its' unknown nature. While treatment is not complex, ruling out other causes, and working with unknown diseases is best done by an experienced clinician.

Treatment Scope and Resourcing

Both best and worst cases rely on space anticipation glasses and repeat testing. These will not be needed for every astronaut but we cannot know which ones will require them so it makes sense to include these as part of the medical system.

The visual changes appear to be variable but consistently hyperopic so specific lens types and correction factors should either be discussed on an individual basis preflight OR a variable power lens included that can accommodate the varied shift. At the present time there are no commercially available lenses of this type on market so no single recommendation can be made.

Communications and Support Needs;

Communications are not expected to be necessary beyond the routine medical ground communications given the context of vision changes in spaceflight and the apparent lack of emergent pathology requiring immediate intervention. However, it is expected that routine ground communication will be present and available to assist with diagnosis and 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 RECONCILATION COMMENTS

The IMM CLIFF for Visual Impairment and/or Increased Intracranial Pressure (VIIP) was the previous name for this medical condition. This CLIFF was made at a time when even less was understood about this disease process than we understand now. Incidence was based on subjective visual changes among crew members which is less reliable than OCT measurements of TRT, now considered the gold standard for this condition. Optic disc edema was also removed from the diagnosis of SANS as it has extremely poor inter-rater reliability on review of imaging. Duration of this condition ranged from 3-28 days but it is unclear where this range originated. LOCL and RTDC were also determined to be 0 in this condition.

LIMITATIONS SUMMARY

•The definition of SANS has changed over time as we have understood more about this disease. The definitions used here were created during the development of this CLIFF and are up to date but also likely to be inaccurate over time as more research is spent understanding the pathophysiology of SANS. •Many of the ocular abnormalities found in flight have unclear clinical significance. Some members with substantial changes to retinal thickness do not have any visual changes and vice versa some members with limited abnormal findings do report visual changes •Progression of SANS is unknown. There is concern that over time vision will continue to worsen however this has not been identified in the data thus far. Long duration missions such as our DRM may have a higher incidence and impact of SANS than the shorter duration missions that were the source for our data. •The dataset for this condition is limited to a small number of individuals as it is a spaceflight specific condition and protected under LSAH for astronaut health privacy •28 of the 34 person missions studied had complete testing. Incomplete testing was removed as was any return fliers as we do not know if having SANS increases a crew member's likelihood of having it on subsequent missions. The total unique astronauts used was 27 •Mission duration also appears to have an impact on incidence of SANS however there are reports of visual changes among shuttle astronauts which implies a relatively rapid onset of these findings of less than 14 days in the microgravity environment. However, within this dataset 60d is shortest mission duration and 1y is the longest. It is unclear what changes are expected after very long duration flight (>1year). There is debate whether these changes will plateau or continue to worsen. •The worst-case definition was agreed upon with the SANS research group. It includes the criteria "choroidal folds involving the retina" and "visual field defects" which are theoretical severe outcomes but have never been observed. The 3rd criterion "TRT>200 microns" was in an astronaut with limited visual changes and no increase in ICP. As discussed, the severity or long-term changes associated with SANS are unknown and thus criteria from our WC scenario may not be possible or clinically relevant. •The effect of partial gravity on the development of SANS is unknown. In our DRM as well as future lunar and mars missions it is unknown whether crew members visual changes will improve with partial gravity. In this CLIFF we have determined that a once a crew member is diagnosed with SANS they will continue to have this condition until a minimum of R+6mo and thus cannot suffer from this condition twice however this may not accurately reflect the disease process. •Duration of the CP2 of this condition was determined to range from 0-12 hours however this may not accurately represent the treatment time of this condition. There is no treatment for SANS other than visual correction with glasses. There also does not appear to be elevated ICP associated clearly with this condition and thus no interventions required to prevent hydrocephalus. Thus the CP2 of this phase will be extremely short. 12 hours was included as the maximum to account for time spent observing the patient, finding necessary equipment, and time to return to work. •OCT testing occurs preflight 6-9 months then at regular intervals throughout flight (L+30, L+90, R+1/3, R+ 30 etc...). These intervals are determined by the operations team and may change over time depending on mission parameters. During ISS missions these tests did not occur within the first week due to other priorities in flight and thus the minimum time to onset of visual changes is unknown but assumed to be less than 14 days as many shuttle astronauts had findings of SANS post flight.

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		
Treated Best Case (TBC)					854							
Untreated Best Case (UTBC)					854							
Treated Worst Case (TWC)		664			854							
Untreated Worst Case (UTWC)		664			854							
	Affected HSTCs (Continued)								TI Calculation			TI Score
	Hand (Dom)	Hand (Any)	Upper Extremity	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)									854	3763	0.226947	22.6947
Untreated Best Case (UTBC)	132							211	1197	3763	0.318097	31.8097
Treated Worst Case (TWC)	132							211	1861	3763	0.494552	49.4552
Untreated Worst Case (UTWC)	132							211	1861	3763	0.494552	49.4552

Clinical Phase 3: Condition End State												
	Affected HSTCs											
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU		
Treated Best Case (TBC)												
Untreated Best Case (UTBC)					854							
Treated Worst Case (TWC)												
Untreated Worst Case (UTWC)					854							
	Affected HSTCs (Continued)								TI Calculation			TI Score

	Hand (Dom)	Hand (Any)	Upper Extremity	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)									0	3763	0	0
Untreated Best Case (UTBC)									854	3763	0.226947	22.6947
Treated Worst Case (TWC)									0	3763	0	0
Untreated Worst Case (UTWC)	132							211	1197	3763	0.318097	31.8097

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 requring use of the alimentary sytem, 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 Condiltion 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.

REFERENCES

Reference
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ACRONYMS

ACRONYM	PHRASE
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