

Clinical Finding Form (ClIFF)

Branch

Baseline

ICL23_Cerebrovascular Accident

A Cerebrovascular Accident is the sudden impairment or loss of consciousness, sensation, and voluntary motion that is caused by rupture or obstruction (as by a clot) of a blood vessel supplying the brain, and is accompanied by permanent damage of brain tissue. Symptoms of stroke include numbness or weakness on one side of the body or face, confusion, impaired speech or vision, loss of coordination or balance, trouble walking, or severe headache.(Merriam-Webster Medical Dictionary, 2021). About 87% of all strokes are ischemic, and defined as when a vessel supplying blood to the brain is obstructed. A hemorrhagic stroke is defined as when a weakened vessel ruptures and bleeds into the surrounding brain which then accumulates and may compress the surrounding brain tissue. 13% of strokes are hemorrhagic (of which 10% are intracerebral (ICH) and 3% are subarachnoid (SAH) (American Stroke Association [AHA], 2021). A Transient ischemic attack (TIA) is a brief episode of cerebral ischemia that is usually characterized by temporary blurring of vision, slurring of speech, numbness, paralysis, or syncope and is often predictive of a serious stroke (Merriam-Webster Medical Dictionary, 2021). It is worth noting that micro-gravity encourages a cephalad fluid shift. It is unclear whether this increases intracranial pressure, but studies have shown that it does at least increase intraocular pressure; often well into ranges usually associated with glaucoma, and also intrajugular venous pressure. Therefore one might expect a hemorrhagic stroke in microgravity to have a worse outcome than in Earth gravity.

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

There are no studies that document the occurrence of cerebrovascular incidence in flight. The space literature included in the incidence data looked at the incidence of cerebrovascular accident in astronauts, ; however, these studies looked at the incidence of stroke over the course of the astronaut's life. Oftentimes, these strokes occurred later on in life at a mean age of 70, so this data may not directly apply to the younger astronaut population (LaPelusa et al. 2016). It was also found that spaceflight does not increase the incidence of stroke in the astronaut population when compared to the non-astronaut group (Ade, 2017).

ANALOG LITERATURE

Only one analog paper was found, and this investigated the incidence of stroke in the passengers and crewmembers of a cruise ship that sailed in remote regions (Carron et al. 2018). While this may be applicable to the astronaut population in that remote regions were involved, the median age of the passengers was 68, which does not reflect the age or health status of the astronaut population. Therefore, this paper was not directly included in incidence calculation.

TERRESTRIAL LITERATURE

Of the two terrestrial articles included in this incidence search, one looks at the incidence of stroke in the global population, correlated with the mean income level of the country (Feigin et al. 2014). The other examined the incidence of stroke in four U.S. communities (Koton et al. 2014). While excellent overviews of stroke risk in large populations, both of these studies may not be directly applicable to the astronaut population due to age and prevalence of cardiovascular risk factors.

OVERALL INCIDENCE SUMMARY

INCIDENCE

mean 2.259E-4 and SD 2.247E-4

INCIDENCE SUMMARY

Spaceflight – (Ade, 2017) – Incidence rate of cardiovascular disease end points in the National Aeronautics and Space Administration Astronaut Corps. 5 events. IR 0.73E-3. This means 6849.315 person-years. Includes retired astronauts. • Spaceflight (LePelusa, 2016) A Cerebrovascular Accident Incidence in the NASA Astronaut Population. 9 events between 1959 and 2014. Includes retired astronauts. Does not have person-years. • Spaceflight – Active Astronauts – HSRB CR SA-03267 – Risk of Cardiovascular Adaptation Contributing to Adverse Mission Performance and Health Outcomes (Cardiovascular Risk) (Baseline), approved 5/13/21. 1 events over 4430 person-years. IR: 2.257E-4 (95%CI: 0.1129E-4, 11.13E-4). Is limited to active astronauts only. Recent HSRB data on strokes included, i.e. astronaut active careers, as it is most representative of fliers.

TABLE 1. INCIDENCE MODEL

Incidence Details

Incidence Type

General

Segment

All

Env. Exposure

NA

Sex

Any

Crowns

Any

Contacts

Any

Pregnancy

Any

Incidence Distribution

Occurrence Dist

Poisson

Incidence Dist.

Gamma

Mean

0.000225898

SD

0.000224699

Gamma

(Shape): 1.0107

(Rate): 4474.15

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Ade, 2017	Spaceflight	4
LaPelusa, 2016	Spaceflight	4
Feigin, 2014	Terrestrial	3
Koton, 2014	Terrestrial	3
Carron, 2018	Analog	3

(Ade, 2017 and LaPelusa, 2016) look at the astronaut population specifically, so the data in these studies is relevant for our purposes. Thus, these two papers have been graded a 4. However, the other three papers (Feigin, 2014; Koton, 2014 and Carron, 2018) look at a broader population that may not necessarily be applicable to the astronaut population. Due to this, the overall LOE grade for these papers has been downgraded to a 3. The sources are all reliable, published in reputable journals. The environment spaceflight environment should be similar to the terrestrial environment for stroke.

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

All mission assigned crewmembers for mission durations of 30 days or more are required to undergo the following monitoring: • 24-hour Holter Monitoring at L-365 days and as clinically indicated. (NASA, MedB 1.7) • Exercise treadmill testing ages 30, 35, 40; every two (2) years between ages 40-50; every year after age 50 (NASA, MR089S). When flight assigned at L-180 days and L-30/45 days (NASA, MR006L). • Cycle ergometer aerobic fitness testing: annually, L-12mo, L-90/30d, FD14, FD75, R-14, R+5, R+30 and as clinically indicated (NASA, N3.07). • Resting ECG annually ((NASA, MR089S). When flight assigned, pre- and post-flight resting ECG at L-9/6 months to L-10 days and R+0/3 days (NASA, MedB 1.6). • Heart-rate monitoring for 2 weeks during exercise training at L-1year, L-45 to L-15 days. In-flight heart-rate monitoring occurs during the first 2 weeks of every mission during every treadmill and cycle ergometer session, as well as during periodic fitness evaluation (PFE) sessions. Thereafter, in-flight heart rate monitoring occurs during each (PFE), while exercising on the Russian cycle ergometer, or during contingencies. (NASA, MR019L) • Pulmonary function testing annually (NASA, MR089S). • C-Reactive Protein testing at L-45/30, R+0, R+3/7, and R+30 for long-duration flights (NASA, MR010L). • Coronary artery CT scanning to obtain Coronary Artery Calcification (CAC) score. "

BEST CASE SCENARIO DEFINITION

A transient ischemic attack (TIA), or mild stroke, with no significant neurologic impairment.

WORSE CASE SCENARIO DEFINITION

A stroke that causes significant permanent neurologic impairment, negatively affecting mission objectives.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

Transient Ischemic Attack

BEST CASE/WORST CASE PROBABILITY COMMENTS

A total of 9 CVA events occurred in 338 NASA astronauts that were selected for this study (LaPelusa, 2016). Of these 9, 3 were TIAs, 3 were ischemic strokes, and 3 were life-ending strokes of unknown origin. For the best case probability, 3 TIAs/9 total CVA incidents was used for a percentage of 33%, and 6/9 total CVA incidents was used for a percentage of 67%.

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

Citation	Source	LOC Value
LaPelusa, 2016)	Spaceflight	4

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 2.259E-4 and SD 2.247E-4	33 - 33	100	0.9	54.4823	0.03	24	9.11507	100	100	0	1.2
Treated Worst Case (TWC)		67 - 67	100	0.9	73.4122	4320	12960	46.8243	100	100	4.9	10
Untreated Best Case (UTBC)	N/A	N/A	N/A	0.9	54.4823	0.03	24	9.11507	100	100	0	1.2
Untreated Worst Case (UTWC)	N/A	N/A	N/A	0.9	100	4320	12960	100	100	100	16.5	19.2

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

Best case scenario definition is a TIA while a worse case scenario definition is a moderate/severe stroke that results in neurologic deficits. For the best case, a TIA is self-resolving without treatment, but will require long-term medical management to reduce the risk of future events.. Standard of care is that ischemic CVA's require hospitalization and treatment with thrombolytics for more severe presentations, if the patient presents within an appropriate time window. If treated with thrombolytics, there is a commensurate risk of bleeding. All of this must be taken into consideration for spaceflight, where the resources will be limited and appropriate diagnostic tools will not be available. CT and MRI are standards of care for the diagnosis of stroke (and determining ischemic vs. hemorrhagic), which will not be available. These limitations will present challenges when it comes to diagnostics and therapeutics in flight.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

Best case is defined as a TIA. The maximum TBC duration was determined to be 24 hours based on the clinical definition of TIA, and could be as low as 0.03 hours (Duca, 2016). In terms of TIA presentations, most patients present to the ED after symptoms have already resolved, and some patients fail to seek medical treatment for a TIA at all. The RTDC was pre-determined to be 100%. The LOCL was determined to be anywhere between 0-1% (Rutten-Jacobs, 2013). TIAs are self-resolving without treatment and do not result in death unless other more severe strokes or cardiac events occur after the TIA.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

Worst case was defined as a moderate/severe stroke resulting in neurologic deficits. TWC duration was found to be anywhere between 4320 hours (6 months) to 12960 hours (18 months) (Hankey, 2007). Greatest improvement in neurologic deficits often occur within the first 6 months, but improvements may occur up to 18 months-- especially with aggressive therapy (PT/OT). (Hankey, 2007) only looked into duration of symptoms for as long as 18 months; data was not collected past this time. RTDC was pre-determined to be 100%; as all stroke cases will require medical intervention and risk recurrent events. LOCL was determined to be anywhere between 4.90% to 10.00% (Heuschmann, 2004; Xian, 2011; Koton, 2004).

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

Best case is defined as a TIA. The maximum WBC duration was determined to be 24 hours based on the clinical definition of TIA, and could be as low as 0.03 hours (Duca, 2016; Easton, 2009). The same data used for TBC duration was used for UTBC duration because TIAs are self-resolving and patients often present to the ED after symptoms have already resolved, equating to a TBC scenario in actual presentation and treatment. The RTDC was pre-determined to be 100%. The LOCL was determined to be anywhere between 0.5 (Johnston, 2020) -1.2% (Rutten-Jacobs, 2013). TIAs are self-resolving without treatment and do not result in death in an of themselves, although predict a risk of further CVAs.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

Worst case was defined as a moderate/severe stroke resulting in neurologic deficits. UTWC duration was found to be anywhere between 4320 hours (6 months) to 12960 hours (18 months). The same data for TWC duration was used for UTWC duration because (Hankey, 2007) combined placebo and treatment groups into one cohort. Greatest improvement in neurologic deficits occurred within the first 6 months, but improvements still occurred up to 18 months. (Hankey, 2007) only looked into duration of symptoms for as long as 18 months; data was not collected past this time. RTDC was pre-determined to be 100%; all stroke cases will require medical intervention and risk recurrent events. LOCL was determined to be anywhere between 16.50% to 19.20% (Emberson, 2014; De Deyn, 1997).

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

Citation	Source	LOC Value
Duca, 2016	Terrestrial	3
Easton, 2009	Terrestrial	
Hankey, 2007	Terrestrial	

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
N/A	N/A	3

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Rutten-Jacobs, 2013	Terrestrial	3
Heuschmann, 2004	Terrestrial	
Xian, 2011	Terrestrial	
Koton, 2014	Terrestrial	
Johnston, 2020	Terrestrial	
Johnston, 2018	Terrestrial	
Embersen, 2014	Terrestrial	
De Deyn, 1997	Terrestrial	

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope Overview Cerebrovascular accident encompasses transient ischemic attack, hemorrhagic stroke, and ischemic stroke. CNES: Transient Ischemic Attack Diagnostic Scope and Resourcing: In the best-case and worst-case scenario diagnosis is based on history and physical examination (neurologic, cardiopulmonary, fundoscopic and vital signs). CT/MRI will be unavailable in-flight. Ultrasound (US) was scoped for carotid US and echocardiogram post-CVA. An attempt at trans-cranial US could be made, but this is a technically challenging US task, even for those with prior soft-tissue ultrasound experience. Thus, it was not scoped in the clinical phase 1 diagnostic capabilities. This may be a consideration for future efforts. Since brain imaging cannot be performed in-flight to assist in determining whether a CVA is hemorrhagic or ischemic, thrombolytic therapy for ischemic CVA was felt too risky by the CRT working group and was thus considered outside the treatment scope for this CRT. The following terrestrial standard of care labs were also not scoped into this CRT: CBC, PT/INR, and PTT because their primary purpose is to assess the safety of thrombolytic therapy administration terrestrially. Troponin is typically obtained terrestrially for differential diagnosis purposes. In the event that a crewmember was to experience an aortic dissection, there would be no treatment interventions available in-flight. An EKG will be performed to assess for the differential diagnosis of myocardial infarction, but troponin was not felt to be critical, and was thus also not scoped into this CRT. Crewmembers are not suspected to be diabetic based on rigorous pre-flight screening but point of care glucose was scoped since CVA can result in elevated glucose levels. Clinical Phase 1 Duration and Rationale This version of IMPACT presumes physician level knowledge, skill, and ability will be present on the mission. This CRT includes a scope of practice code of 5 (which correlates to an "Experienced procedure trained generalist attending (e.g. ED attending).") The CRT working group SME consensus Clinical Phase 1 duration: Best Case CP1: 0.90 hours Worst Case CP1: 0.90 hours Treatment Scope and Resourcing: For the best-case scenario of a mild stroke or TIA with no significant neurologic impairment treatment would consist of neurologic checks, dual anti-platelet therapy, carotid ultrasound, and possible trans-cranial ultrasound. Lipid lowering would likely be pursued empirically as lipid laboratory capabilities are outside the scope of this CRT. Anti-hypertensive treatment is scoped into this condition as a secondary prevention method since hypertension is not currently a condition in the ICL 1.0. The regimen selected is based on the Aerospace Medicine Board approved Clinical Practice Guideline at the Johnson Space Center (1st line telmisartan, 2nd line adds amlodipine, 3rd line adds chlorthalidone). Physical therapy is not scoped into the treatment in the best-case scenario since, by definition, there is no lasting neurologic impairment. For the worst-case scenario of a stroke causing significant permanent neurologic impairment, thrombolytic therapy was considered outside the scope of this CRT (considered to be too much of a risk without the ability to obtain intracranial imaging to confirm hemorrhagic vs. ischemic stroke). Intravenous access, IV hydration and IV labetalol for blood pressure management in the first 48 hours, and IV diazepam for seizure in the setting of intracranial hemorrhage have been included in this CRT. Neurologic checks and antipyretics (acetaminophen) have also been included. The convalescent management after a worst-case stroke included a swallow study, aspirin for secondary prevention, carotid, cardiac, attempted trans-cranial ultrasound, management of hypertension (same regimen as best-case scenario), empiric lipid lowering, and physical therapy. Hyperglycemia due to diabetes mellitus is not anticipated given rigorous pre-flight screening of crewmembers. However, hyperglycemia can occur as a result of CVA and outcomes are improved with treatment. An insulin drip was considered outside the scope of this CRT, so hyperglycemia will be treated with subcutaneous dosing of insulin. Platelet transfusions and clotting factors will not be available in-flight for treatment. Use of a lower extremity pneumatic compression device is a Class A recommendation for thromboprophylaxis in the setting of hemorrhagic CVA according to the American Heart Association. Due to the cephalic fluid shift in microgravity, the efficacy of pneumatic compression devices is unknown in spaceflight. Concerns for mass/volume constraints led the CRT working group to determine that pneumatic compression devices were outside the scope of this CRT. Note, compression stockings are not advised as an alternative in AHA stroke guidelines. Communications and Support Needs: For both best and worst-case scenarios communications with ground specialists to facilitate treatment and healing was considered necessary given the limited diagnostic and treatment capabilities in-flight. References 1. Furie KL, Rost N.

Overview of secondary prevention of ischemic stroke. 2021 Retrieved from [https://www.uptodate-com.libux.utmb.edu/contents/overview-of-secondary-prevention-of-ischemic-stroke?sectionName=Low-density%20lipoprotein%20cholesterol%20\(LDL-C\)%20lowering%20therapy&search=CVA%20treatment&topicRef=1126&anchor=H13&source=see_link#H13](https://www.uptodate-com.libux.utmb.edu/contents/overview-of-secondary-prevention-of-ischemic-stroke?sectionName=Low-density%20lipoprotein%20cholesterol%20(LDL-C)%20lowering%20therapy&search=CVA%20treatment&topicRef=1126&anchor=H13&source=see_link#H13) 2. Hemphill CJ, Greenberg S, Anderson CS, Becker K, Bendok B, Cushman M, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. Stroke. 2015; (46):2032–60 3. Oliveira-Filho J, Mullen M. Initial assessment and management of acute stroke - UpToDate. Date. . 2021 Retrieved 14 May 2021 from https://www.uptodate-com.libux.utmb.edu/contents/initial-assessment-and-management-of-acute-stroke?search=CVA%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H95644450 4. Oliveira-Filho J, Samuels OB. Intravenous thrombolytic therapy for acute ischemic stroke: Therapeutic use. Date. . 2020 Retrieved from https://www.uptodate-com.libux.utmb.edu/contents/intravenous-thrombolytic-therapy-for-acute-ischemic-stroke-therapeutic-use?search=administering%20alteplase&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2 5. Powers William J., Rabinstein Alejandro A., Ackerson Teri, Adeoye Opeolu M., Bambakidis Nicholas C., Becker Kyra, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019; 50(12):e344–418 6. Bedside Assessment of Swallowing. Retrieved 15 May 2021 from <https://www.d.umn.edu/~mmizuko/5200/bedside.htm> 7. Valium, Diastat (diazepam) dosing, indications, interactions, adverse effects, and more. Retrieved 15 May 2021 from <https://reference.medscape.com/drug/valium-diaostat-diazepam-342902> "

IMM CLIFF RECONCILIATION COMMENTS

The most recent references from IMM CLIFF on CVA/Stroke were from 2012, so this most recent iteration greatly improves contemporary understanding of stroke risk in spaceflight. (Ade, 2017 and LaPelusa, 2016) look at spaceflight risk specifically, via astronaut populations and the LSAH, so these two studies greatly increases the literatures contribution to risk assessment. Furthermore, multiple studies looking at aggregate stroke risk have been published in this interval, and therefore the CPIL and LOCL data reflect this new understanding.

LIMITATIONS SUMMARY

Outcomes from strokes vary widely, and the wide margins of CP2 durations reflect this uncertainty. While the baseline health of the astronaut corps would pre-dispose for a shorter convalescence, the anatomy of a CVA (ex: ischemic penumbra) would be the driving factor in task impairment-- nevertheless, the necessity of a wide range of functional outcomes remains a significant limitation in this risk assessment. RTDC probability was assigned 100% for both minimum and maximum for all scenarios. Regarding best-case scenarios, there are cases of CVA/TIA that are only treated with medical optimization. However, given the risk of recurrent events, even one documented event would likely merit an 'RTDC event,' despite a potentially negligible impact upon mission operations.

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)	223	664	113	89	854	44	145	5	13			
Untreated Best Case (UTBC)	223	664	113	89	854	44	145	5	13			
Treated Worst Case (TWC)	223	664	113	89	854	44	145	5	13	6		
Untreated Worst Case (UTWC)	223	664	113	89	854	44	145	5	13	6		
	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)	132	564	414	22	196	34	34	211	3757	3763	0.998406	99.8406
Untreated Best Case (UTBC)	132	564	414	22	196	34	34	211	3757	3763	0.998406	99.8406
Treated Worst Case (TWC)	132	564	414	22	196	34	34	211	3763	3763	1	100
Untreated Worst Case (UTWC)	132	564	414	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		
Treated Best Case (TBC)												
Untreated Best Case (UTBC)												
Treated Worst Case (TWC)		664		89								
Untreated Worst Case (UTWC)	223	664	113	89	854	44	145	5	13	6		
	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)	132							211	343	3763	0.0911507	9.11507
Untreated Best Case (UTBC)	132							211	343	3763	0.0911507	9.11507
Treated Worst Case (TWC)	132		414	22	196		34	211	1762	3763	0.468243	46.8243
Untreated Worst Case (UTWC)	132	564	414	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: Depends on where the stroke occurs in the brain; for the purpose of TI, we are taking the middle ground for WC as hemiparesis.

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.

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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