Clinical Finding Form (CliFF)

Branch: Baseline

ICL83_Seizures

A seizure is generally defined as uncontrollable electrical signals in the brain that cause sudden onset physical effects in the body, which can include unconsciousness or unresponsiveness, shaking of limbs or the entire body, behavior changes, emotional changes, and many other symptoms. There are many categories of seizures. Specifically for healthy astronauts in spaceflight, we are concerned for new onset unprovoked seizures as well as prolonged seizures, known as status epilepticus. New onset implies the astronaut has never had a seizure, nor been diagnosed with a seizure disorder. Unprovoked means that the seizure occurred spontaneously and without any identifiable inciting factor, such as meningitis, a head injury, chemical, toxic, or environmental exposure.

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

(Gilkey, 2012) estimated the incidence of first unprovoked seizure in spaceflight via a Bayesian analysis utilizing incidences from the astronaut corps and a large terrestrial epidemiological study. A mean incidence rate of 0.000270 events per person-year with standard deviation of 0.0000288 was estimated. This was an average of the incidences for males and females, as there was a slight (but clinically insignificant) difference between the two genders. Terrestrial data for this estimate was averaged from three age ranges: 40-44, 45-49, and 50-54, yielding an average age of 47 years. The error factor was estimated to be 1.19 from a 95% confidence interval constructed from male and female data from population age 40-54 years (Gilkey, 2012). The pre-flight astronaut corps had zero seizures in 2235.2 person-years. The mean incidence rate of seizure in this population was estimated at 0.00027 events per person-year. Standard deviation is 0.0000288. 95% Confidence Interval is 2.25 x 10e-4 – 3.19 x 10e-4 (Gilkey, 2012). Limitations include assuming an average incidence rate of seizure irrespective of environmental conditions and the cause of seizure, and the calculation of the error factor was determined using epilepsy data, not unprovoked seizure data, as the paper did not have confidence interval information on first unprovoked seizure data. Additionally, data regarding repeated occurrences of seizures could influence the predicted rate of incidence since it is known that the occurrence of a single seizure increases the likelihood of subsequent seizures. Use should be treated with understanding of these limitations; however, it is likely a reasonable representation of the rate of seizure incidence given the occurrence data available and given the assumptions made during construction of the estimate (Gilkey, 2012).

ANALOG LITERATURE

In a study population which included all individuals who served in active components of the Army, Navy, Air Force, or Marine Corps, incidence of seizures was found to be 9.1 events per 10000 person-years for deployed members without TBI (Bytnar, 2017). Data were retrieved from the Defense Medical Surveillance System (DMSS) from records of both ambulatory encounters and hospitalizations of active component members of the U.S. Armed Forces. The secondary analysis included members deployed during OEF, OIF, or Operation New Dawn (OND). For those in the study who reported a TBI, there was an incidence of 12.9 per 10000 person years for seizures. Men had a lower incidence of seizures than women (11.9 vs 18.6 events per 10000 person years); with minimal clinical difference, the mean was used as a reasonable approximation of incidence. (Bytnar, 2017). More relevant to the astronaut population, the rate of seizure in deployed aircrew (a medically pre-screened population) was reported to be 0.9 events per 10,000 person-years. This was not a primary outcomes and no additional information was reported about this group. An analysis of data collected on US Navy Polaris submarine patrols over the ten year period 1963-1973 reported a total of 1685 medical events treated. Illness rates are indicated as new/cases/1000 man-days. There were 53 neurological events during this period. There were three seizures; one of unknown etiology caused one sick day, one grand mal epilepsy caused 2 sick days, and one post traumatic epilepsy caused 7 sick days. Illness rate and rate of days lost were significantly higher than those observed in the surface population (P <0.05) (Tansey, 1979). This study estimates an event rate per person year of 0.0000007 (3 seizures/4,410,000 person-days). Four evacuations occurred during the study period but there is no information by condition.

TERRESTRIAL LITERATURE

Unprovoked seizures are seizures occurring in the absence of identifiable precipitating factors (Hauser, 2008). Unprovoked seizures may be single or recurrent. The incidence of acute symptomatic seizures from all causes is 29-39 per 100,000 person-years. Traumatic brain injury, cerebrovascular disease, drug withdrawal, stroke, and metabolic insults are the commonest causes. The incidence of single unprovoked seizures is 23-61 per 100,000 person-years. Single unprovoked seizures predominate in men and in patients less than 12 months and older than 65 years (Hauser, 2008).

OVERALL INCIDENCE SUMMARY

INCIDENCE

Mean 2.70E-4
SD 2.88E-4

INCIDENCE SUMMARY

From the GRC Bayesian modeling of astronaut data using terrestrial sources for informing the priors, the posterior distributions for the incidence rate of seizures is log-normally distributed with mean 2.70E-4 and SD 2.88E-4. Evidence for the incidence comes from (Gilkey, 2012) - Bayesian analysis of inflight, preflight, and terrestrial incidence data. Posterior distribution defined as log-normal with the following parameters. Since this condition utilizes the results of a Bayesian analysis, the posterior distribution can be expressed directly through the reported parameters.

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.
Log-Normal

Mean
0.00027

SD
0.000288

Log-Normal
(Mean): 0.00027
(SD): 0.000288

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Gilkey, et al. 2012	Spaceflight	4
Bytnar, et al. 2017	Analog	3
Hauser, et al. 2008	Terrestrial	2
Tansey, et al. 1979	Analog	3

(Gilkey, 2012) is the best estimate of spaceflight incidence since it was specifically designed to address this issue. Gilkey utilized data from the pre-flight astronaut corps as well as a large terrestrial study to calculate the risk of seizure in spaceflight. Limitations exist, but are well-explained and incorporated into the estimate. (Tansey, 1979) is a relevant analog population of medically screened submariners; however the data is quite old and during a different era of medical assessment and treatment. Of the three seizures reported, one was post-traumatic and one was "unknown." The incidence here was strikingly low across ten years. (Bytnar, 2017) is a study of a large military population to determine seizure incidence in

those with and without a history of head trauma. The incidence of seizure without TBI was quite high in the general population, and included members with prior seizure history and many other unknowns in the deployed and non-deployed populations. However, the incidence of seizure in deployed pilots and aircrew was much lower, and the incidence from this medically screened population is more reflective of the astronauts' risk. (Hauser, 2008) was cited in dynamed as the main source for incidence in the general population. It is a well done and large study but has all of the limitations of non-selected all-age population incidence data. The lower bound of the incidence range approaches that of the Gilkey data, but the range is quite wide overall.

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

Disqualifying conditions include: any neurologic disorder that may interfere with the performance of duties; tumors of the nervous system; vascular disorders of the nervous system (e.g. arteriovenous malformation, intracranial aneurysms, familial cavernous angioma, and temporal arteritis). Sporadic cavernous angiomas require neurologic evaluation. History of cerebrovascular accident (stroke, TIA, or subarachnoid hemorrhage). Asymptomatic disease of the carotid or vertebral arteries requires neurologic evaluation. Seizure disorders or history of seizure disorders, including absence seizures. History of traumatic brain injury with associated intracerebral hemorrhage with persistent neurologic deficits; or intracranial hemorrhage requiring surgery or with persistent neurologic deficits (e.g. subdural or epidural hematoma). (International Space Station Program, 2009); (NASA, 2007) (International Space Station Program, 2009) No preventative treatment or seizure prophylaxis is indicated for healthy individuals. No testing exists that can detect a higher risk of unprovoked seizure in an otherwise healthy individual.

BEST CASE SCENARIO DEFINITION

A single seizure that resolves spontaneously or responds to drug therapy and does not recur.

WORSE CASE SCENARIO DEFINITION

Status epilepticus (a seizure lasting longer than 5 minutes, or ≥2 discrete seizures between which there is incomplete recovery of consciousness).

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

Status Epilepticus

BEST CASE/WORST CASE PROBABILITY COMMENTS

(Aminoff, 1980) focuses on epileptic patients with possible conversion of seizures to status epilepticus. The etiology, clinical features, and outcome of generalized major motor status epilepticus in 98 patients over the age of 14 years were reviewed. The precise incidence of status epilepticus in the epileptic population is uncertain, but a figure of 1 to 5 percent was given. An estimate of incidence for a healthy population may be less than this. The others have seizures that do not recur (Aminoff, 1980). According to (Betjemann, 2015), the incidence of status epilepticus is 10–41 per 100,000 in a general population for a percent of 0.01-0.041% per year.

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

Citation	Source	LOC Value
Aminoff, et al. 1980	Terrestrial	2
Betjemann, et al. 2015	Terrestrial	2

(Aminoff, 1980) study focuses on epileptic patients and the likelihood of conversion of seizures to status epilepticus. The etiology, clinical features, and outcome of generalized major motor status epilepticus in 98 patients over the age of 14 years were reviewed. The precise incidence of status epilepticus in the epileptic population is uncertain, but a figure of 1 to 5 percent was given. The others have seizures that do not recur (Aminoff, 1980). Given that this is terrestrial data in epileptic patients, the LOC value is a 2 as this data is less applicable to space travel and astronauts who were screened for pre-exsting seizure disorder. According to (Betjemann, 2015), the incidence of status epilepticus is 10–41 per 100,000 in a general population for a percent of 0.01-0.041% per year; again, this includes all comers and those with existing seizure disorders; this study does incorporate the baseline population incidence rate, which Aminoff does not.

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 2.70E-4 SD 2.88E-4	85 - 99	100	1.75	54.5575	0.008	0.08	9.11507	0	0	0	0
Treated Worst Case (TWC)		1 - 15	100	1.75	54.5575	0.08	204	9.11507	100	100	3	35
Untreated Best Case (UTBC)	N/A	N/A	N/A	1.75	54.5575	0.008	0.08	9.11507	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	1.75	100	0.08	204	100	100	100	17	38

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

Terrestrially, new onset seizures are typically evaluated and treated in the emergency department. The majority of simple seizures resolve quickly, often within a few minutes, and by definition the patient is no longer seizing at the time of arrival to the hospital. Evaluation of single brief seizures is variable, and can include history and physical examination (including detailed neurological examination), laboratory testing, and CT imaging of the brain. An MRI or EEG is not performed in the emergency department, but could be accomplished if the patient is admitted to the hospital. In general, patients with simple brief seizures with a normal clinical evaluation will be discharged with primary care or neurology follow-up. No antiepileptic (anti-seizure) medications are started after the first seizure, as recurrence is uncommon. Prolonged seizures or status epilepticus cases are true emergencies and require emergency department evaluation and treatment. These patients are often transported by ambulance, and if so, may have treatment started before arriving at the hospital. Immediate history and physical examination are performed along with prompt initiation of IV or intramuscular antiepileptic medications. Additional doses of the initial medication and/or doses of secondary and tertiary medications are administered if seizing continues. The most severe and refractory cases can require heavy sedation, paralysis, and endotracheal intubation in order to protect the airway and facilitate additional treatment. Severe patients will be admitted to the ICU. MRI and EEG are often performed during the admission. Status epilepticus patients are discharged on antiepileptic medications. In spaceflight, the history and neurological examination are readily available, as are limited laboratory tests. CT, MRI, and EEG testing are not available with current technology. Antiepileptic medications can be administered via the IV or IM route. Basic airway management with manual airway opening as well as oral and nasal airway placement are available and may be required given the sedating nature of the medications. In spaceflight, deep sedation, paralysis, and prolonged ventilation are not feasible. RTDC is assured in status epilepticus. It is uncommon for single brief seizures to recur; however, RTDC is possible based on the clinical judgment of the flight surgeon.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

Tonic-clonic seizures can last from a few seconds to a few minutes. In addition, escalation of treatment should be taken when seizure lasts longer than 5 minutes (Al-Shami, 2016). Another study groups recurring seizures and seizures lasting more than 5 minutes in the complicated seizure category, indicating a seizure lasting more than 5 minutes is not a best case scenario (Shorvon, 2012). Thus, by definition, the Best Case scenario duration ends at 5 minutes when the seizure becomes a Worst Case (status epilepticus). Duration therefore is from 30s to 5 minutes. Standardized Mortality Ratio 1.2-2.3 for a single seizure and 1.6-4.1 for unprovoked seizure but irrelevant given definition of best case scenario. Due to the definition of the best case scenario, RTDC and LOCL are both 0%.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

Status epilepticus is defined as a seizure lasting more than 5 minutes and third phase therapy (final phase) begins when seizure continues for > 40 minutes total duration despite initial and second-phase therapy (Glauser, 2016). Another study noted that status epilepticus was harder to break if symptoms had been going on untreated for more than 12 hours (Bonaventura, 2008). (Alkhachroum 2020) studied super-refractory status epilepticus and began their experimental treatment after seizures had been ongoing for an average of 2 days (max of 4 days) despite ICU treatment, and the patients took an average of 2 additional days to improve (a max of 4.5 days). Using the worse case from this study, refractory SE can last as long as 8.5 days. The range for duration is thus between 5 minutes and 8.5 days. Early treatment in the emergency department or intensive care is a key for successful treatment; this is mentioned throughout the guidelines (Brophy, 2012). Thus, all patients with status epilepticus must have immediate treatment in-flight and be returned to definitive care. Loss of life is estimated to be between 3% and 35% depending on which study is cited (JAMA, 1993.)

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

Tonic-clonic seizures can last from seconds (30s mentioned in one paper) to a few minutes. In addition, treatment should be escalated when a seizure lasts longer than 5 minutes (Al-Shami, 2016). One study grouped recurring seizures and seizures lasting more than 5 minutes into the complicated seizure category, indicating a seizure lasting more than 5 minutes is not a best case scenario (Shorvon, 2012). Thus, by definition, the Best Case scenario duration ends at 5 minutes when the seizure becomes a Worst Case (status epilepticus). The duration is therefore 30s to 5 minutes for the untreated condition. Antiepileptic drugs did not affect overall mortality after a first seizure (Leone, 2016) and incidence of seizures causing injury or death in the general population was 32.2 in 100,000, although this includes the worst case scenario. By definition, TBC is a single seizure that resolves spontaneously or quickly responds to drug therapy and does not recur. RTDC and LOCL for the best case scenario is zero regardless of treatment status.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

Expert consensus is that any episode of seizure activity lasting 5 minutes or longer is considered status epilepticus (Pellock 2007) which is a true emergency. Another study noted that status epilepticus untreated for longer than 12 hours was much harder to control (Bonaventura, 2008). (Alkhachroum 2020) studied super-refractory status epilepticus and began their experimental treatment after seizures had been ongoing for an average of 2 days (max of 4 days) despite ICU treatment, and the patients took an average of 2 additional days to improve (a max of 4.5 days). With a max of 8.5 days of continuous status epilepticus in an ICU-treated group, untreated status may last at least this long. As RTDC percent is 100% for the treated condition, the same can be said for the untreated condition. In one study, in the placebo group, 15.7 percent of people died when not treated prior to hospitalization and 1.4% of them died during hospitalization for a total of 17.1% (Alldredge, 2001). Mortality reaches 38% in untreated older adults of 60–79 (Legriel, 2016).

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

Citation	Source	LOC Value
Al-Shami, et al. 2016	Terrestrial	3
Fisher, et al. 2017	Terrestrial	
Shorvon, 2012	Terrestrial	
Glauser, et al. 2016	Terrestrial	
Lowenstein, et al. 1998	Terrestrial	
Bonaventura, et al. 2008	Terrestrial	
Pellock, 2007	Terrestrial	
Alkhachroum, et al. 2020	Terrestrial	

A seizure duration ≥ 5 minutes may be associated with more severe damage seen on neuroimaging (Al-Shami, 2016). Simple seizures can last from a few seconds (30 s mentioned) to a few minutes. In addition, an escalation of treatment should occur when seizures lasts longer than 5 minutes. Status epilepticus is a seizure that last more than 5 minutes (Fisher, 2017) or multiple sezures in a short period. Treatment should be escalated if seizure activity lasts 5 minutes, or if seizure activity recurs without return to baseline between seizures (Shorvon, 2012). Third phase therapy (final phase) begins when a seizure continues for > 40 minutes total duration despite initial and second-phase therapy (Glauser, 2016). The response rate to drugs was less than 40 percent when treatment was begun two hours or more after the onset of the seizures (Lowenstein, 1998). Results showed a worse response to therapy in SE lasting >12h (Bonaventura, 2008). Expert opinion is that any episode of seizure activity lasting 5 minutes or longer should be considered status epilepticus (Pellock, 2007). Alkhachroum (2020) studied super-refractory status epilepticus and began their experimental treatment after seizures had been ongoing for an average of 2 days (max of 4 days) despite ICU treatment, and the patients took an average of 2 additional days to improve (a max of 4.5 days). With a max of 8.5 days of continuous status epilepticus in an ICU-treated group, status epilepticus may last at least this long.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Angus-Leppan, 2014	Terrestrial	3
SIGN, 2018	Terrestrial	
Brophy, et al. 2012	Terrestrial	

Low risk patients with first time seizures typically have no neurological deficits, normal magnetic resonance imaging and electroencephalography, and a 35% risk of recurrence at five years; they are not usually offered treatment or seizure prophylaxis. ICU admission occurs in the case of status epilepticus (Angus-Leppan, 2014). Patients should be admitted to an intensive care unit for close monitoring, multiple antiepileptics (including the potential of general anesthesia), and referral to a specialist within 60 minutes (SIGN publication no. 143). The emergency department or intensive care is a key for successful treatment; this is mentioned throughout the guidelines (Brophy, 2012). LOC 3 given terrestrial data from unselected general population.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Hauser, et al. 2008	Terrestrial	3
Leone, et al. 2016	Terrestrial	
Manno, 2003	Terrestrial	
JAMA, 1993	Terrestrial	
Kirby, et al. 1995	Terrestrial	
Alldredge, et al. 2001	Terrestrial	

Citation	Source	LOC Value
Legriel, et al. 2016	Terrestrial	

Standardized Mortality Ratio 1.2-2.3 for a single seizure and 1.6-4.1 for unprovoked seizure but this is not relevant given the definition of best case scenario (Hauser, 2008). Mortality may be about 20% but can be up to 35% (Manno, 2003), (JAMA, 1993). Antiepileptic drugs did not affect overall mortality after a first seizure (Leone, 2016). Incidence of seizures causing injury or death in the general population was 32.2 in 100,000 (Kirby, 1995). In one study, 15.7 percent of people in the placebo group died when not treated prior to hospitalization and 1.4% of them died during hospitalization for a total of 17.1% (Alldredge, 2001). Mortality may reach 38% in older adults of 60–79 (Legriel, 2016). LOC 3 given all terrestrial data, all adult ages.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope

Overview
First time seizure occurs after an acute insult to the brain. Terrestrially the differential diagnosis of the cause of the seizure can be extremely broad and occur from trauma, ischemia, infection, or metabolic disturbances. In spaceflight this differential will likely be limited due to extensive screening measures of current astronauts. However, the risk of seizure will still exist as a final common pathway of many disease processes. We define the best cases scenario of this condition as a single seizure that resolves spontaneously or responds to drug therapy and does not recur. The worst case definition is defined as Status epilepticus (a seizure lasting longer than 5 minutes, or ≥2 discrete seizures between which there is incomplete recovery of consciousness).

CNES: N/A

Diagnostic Scope and Resourcing
Diagnosis of seizure as opposed to syncope or other abnormal movement or mental status disorders can often be the first and most challenging step. As with most emergent conditions, diagnosis and treatment will be occurring simultaneously.
In the best case scenario, diagnosis is based on history and physical. Often H&P are inadequate to determining the cause of seizure and thus laboratory evaluation of electrolyte derangements is necessary. EKG is included to evaluate for syncope and/or arrhythmia that is often a seizure mimic that has a vastly different approach to treatment.

In the worst case scenario, the approach to diagnosis is the same as the best case scenario as the differences between the definitions scenarios is the length and response to treatment.

In terrestrial standards a first time seizure would involve brain imaging of CT or MRI which is not feasible in spaceflight and was excluded as a diagnostic resource with the assumption that a first time seizure would require imaging upon return to RTDC. Lesions such as masses, intracranial bleeding, CVA, intracranial abscesses, etc... that cause mechanical seizure would not be able to be managed in flight so immediate imaging is not necessary until higher level of care is available. EEG is similar in that it may not substantially change management in flight and thus would not be worth resourcing for this condition. Lumbar puncture was considered as well for diagnosis of infectious etiologies but as with terrestrial care, a high clinical suspicion for meningitis or encephalitis would require treatment in the absence of lumbar puncture and delay of antibiotics for this procedure produces worse outcomes. It was agreed that instead of resourcing the instruments, training, and analytics required for a lumbar puncture that care would be initiated based on clinical suspicion. The antibiotics and antivirals used to treat meningitis and encephalitis are resourced elsewhere

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 hours
CP1 WC (Treated or Untreated): 1.75 hours

The maximum scope of practice for both the best case and worst case scenario is 5 (attending physician) due to the complexity of the condition, severity of the disease process, and long term management of the predisposing condition

Treatment Scope and Resourcing

In the best case scenario, the seizure is aborted spontaneously or after 1-2 doses of benzodiazepines without recurrence. Suction and oxygen are included to reduce the risk of aspiration and hypoxia during seizure or in the immediate post ictal state. Electrolytes are replaced and there is the possibility of initiation of long term antiepileptic medications depending on the circumstances of the event. This is consistent with terrestrial standards.

In the worst case scenario the seizure is not aborted with 1-2 doses benzodiazepines and progresses to status epilepticus. Suction and oxygen are included to reduce the risk of aspiration and hypoxia during seizure or in the immediate post ictal state. Second line abortive seizure medications are included and follow terrestrial guidelines/algorithms for the management of status epilepticus. Resourcing for intubation and sedation is also included for airway protection and inadequate ventilation. Sedation medications with an emphasis on those used for refractory status epilepticus are included. Electrolytes are replaced and there is a high likelihood of initiation of long term antiepileptic medications for maintenance.

Communications and Support Needs

Real-time audio and video loop communication are not necessary for treatment in the best case scenario as seizure resolution would likely occur before consultation could be initiated. However in the best case scenario consultation with mission control and ground specialists in real time would be necessary for optimal management.

REFERENCES
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IMM CLIFF RECONCILATION COMMENTS

The IMM CLiFF and this one share the same estimated incidence of seizure in spaceflight, as both are appropriately based on (Gilkey, 2012). No new spaceflight or analog literature has been published since the IMM CLiFF. At the same time, no seizures have occurred in spaceflight nor in the preflight astronaut corps since then, so the incidence is probably slightly lower than estimated for IMM. The major difference between the CLiFFs is that the duration of all seizures in the IMM CLiFF was a maximum of 48 hours, as it was assumed all astronauts who seized would be evacuated to definitive care. In the case of exploration length missions, this is not always feasible. Given that the Best Case seizures have been shown to infrequently recur and are rarely given ongoing prophylactic antiepileptic drugs, the RTDC of 100% will not be realistic in the setting of missions beyond low Earth orbit. Based on the terrestrial literature, no additional definitive care is required in the Best Case. Recent literature from (Alkhachroum, 2020) informs the Worst Case duration, as status epilepticus can last up to (and likely longer than) 8.5 days, even when treated aggressively in an ICU. This study was not available for IMM, but would not have changed that duration given the 100% RTDC.

LIMITATIONS SUMMARY

There is a significant body of literature for seizures that inform the worst cases, and given that this is a true emergency with significant mortality (and worse outcomes when treatment is started later), the RTDC and LOCL are reliable. In the best case, the data is more challenging, and this will clinically be the hardest issue to manage and disposition in spaceflight. It is uncommon for single unprovoked seizures to recur or become status epilepticus, but that risk is not zero. The literature suggests that RTDC can be zero; however, the risk of keeping an astronaut in orbit for a prolonged period of time is uncertain, and clinically there will be a low threshold to return these astronauts. In the IMM CLiFF, it was assumed 100% of seizure cases would be RTDC, as such, all of the durations ended at 48 hours. This is not the case in an exploration length mission. Clinically, limitations exist for the provision of antiepileptic medications in spaceflight, as the formulary to handle the severe cases is quite large. Sedation is a common side effect, and the ability to safely monitor a sedate astronaut in space and manage airway complications is also limited. There has never been a seizure in spaceflight, nor in the documented preflight astronaut corps. The analog data is variable, and the terrestrial data has all of the limitations of general population studies. The Bayesian analysis from the Gilkey paper from 2012 is the best estimate for spaceflight incidence, although it does have its own limitations as described.

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	6		
Untreated Best Case (UTBC)	223	664	113	89	854	44	145	5	13	6		
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	3763	3763	1	100
Untreated Best Case (UTBC)	132	564	414	22	196	34	34	211	3763	3763	1	100
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)												
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							211	343	3763	0.0911507	9.11507
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 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.

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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