Clinical Finding Form (CliFF)

Branch Baseline

ICL12_Benzodiazapine Or Opioid Overdose

Benzodiazepines (BZD) are sedatives frequently prescribed for insomnia and anxiety. A BZD suppresses the central nervous system by enhancing the effects of GABA (the primary inhibitory neurotransmitter) in the brain (Griffin 2013). Overdosing on BZD often leads to CNS depression, including symptoms such as altered mental status, slurred speech, and ataxia. Severe respiratory depression is uncommon in isolated BZD overdoses, however, concurrent use of other sedatives, such as opiates, can lead to respiratory arrest, which can be treated with the reversal agent flumazenil (Höjer 1989,Garg 2017, Jones 2015). Opioids include pain-relieving prescription medications such as morphine, oxycodone, hydrocodone, fentanyl, hydromorphone and methadone. Opioids interact with opioid receptors in the body producing analgesic effects and can also cause euphoria (Camí 2003). Opioid overdose similarly leads to altered mental status due to CNS depression, but compared to BZD, respiratory suppression is more pronounced and is often fatal without treatment (White 1999). Naloxone is a short-acting opioid antagonist that can be used as initial management of overdose by immediately reversing the opioid effect on the receptor (Bertini 1992) . However, treatment for both BZD and opioid overdose is supportive and the survival of flight crew will be dependent upon having necessary respiratory support and pharmacologic interventions available.

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 is no data regarding incidence of overdose of benzodiazepines or opioids in spaceflight or in astronauts. The spaceflight incidence of benzodiazepine or opioid overdose can be presumed to be far less than the previous reported rate of 2 events in 49.49 person years noted by the prior CLiFF, a lack of a specific denominator precludes the ability to calculate a percentage. This same limitation extends to analog and terrestrial epidemiologic reports. Despite the commonly reported number of events, a comparative total population or "denominator" is rarely disclosed. In the cases where a "denominator" is available it is often a group of individuals who may have coexisting medical conditions, which may be limited in terms of external validity to a more general population. Below is a line-item summary of the deficits of the available literature: Johnston 2011 source - not a publication but rather a ppt presentation of anecdotal reports that is 2 events in 49.49 person years (0.0439) events were not OD events and unsure if they were due to benzodiazepine. Appears that the known spaceflight incidence of benzo or opioid overdose is 0. Putcha 1999 - no overdose events only residual drowsiness in AM from medication side effect. Barger 2014 - Very strong prospective study in the spaceflight population- but no overdose events. 2% of sleep aids taken were benzodiazepine. No direct incidence data regarding overdoses during space-flight was elucidated in the search of the aforementioned databases. Previous reports of adverse medication events during spaceflight range from 12.5 %to 15% (Locke, 2011 and Putcha, 1999) but these cannot be classified as BZD or opioid overdose.

ANALOG LITERATURE

There is limited data regarding the active military population and opioid or benzodiazepine related overdose. There are several documents highlighting the importance of recognizing and preventing overdose from substance misuse and its correlation to mental stressors and mental illness (Headquarters, D.o.t.A., 2012), and reportedly 625 of an unknown proportion of soldiers were treated for overdoses in military emergency departments. Overdoses with intramuscular opioid used during combat surgery have also been noted (Beecher 1944), though this form of medication administration has largely been supplanted by safer alternatives. Similarly, there are reports of opioid overdoses of opioids with treatments utilized in tactical combat casualty care, but incidence in the analogue population is not reported (Butler, 2011). Previous CLiFFs discuss the rate of substance abuse (0.0043 evens/person year), specific incidence of overdoses were not noted. Of the sources, the most reliable is the Hesse 2011 surveillance study of the US Armed Forces who served in an active component of the U.S. military anytime from 1/1/2001-12/31/2010. Total events: 14,979 (105/100,000 person year). Pain medication events: around 6000/14,979. Pain medication poisoning-related hospitalizations incidence: 0.00042/person year in active military. Among these events, pain medications plus sedatives and hypnotics were responsible for around 49% of the total recorded events. An estimated incidence of 0.00051/person year can be calculated based on graphical data from this publication. As pain medications, sedatives, and hypnotics include more than two categories of interest, incidence of opioid and BZD overdose was likely lower than the calculated incidence in this 10 year period.

TERRESTRIAL LITERATURE

Adverse drug events in general, based on FDA reports Age burden of serious events for the 18-44-year-old and 45-64-year old age group were 25.3% and 33.7% respectively. Opioids accounted for the first-ranked cause of death. Study by Jones et al. reported nonmedical use-related ED

visits involving both opioid and BZD to be 34.2 per 100,000 population in 2011. In 2014, the estimated rate of ED visits due to opioid is 177.7 per 100,000 population (0.177%) (Weiss 2016). ED visit rate includes both nonfatal overdoses and mortalities. However, with the rising number of both opioid and BZD overdose deaths, current incidence of overdose is most likely higher. The 2017 data from the National Institute on Drug Abuse reported that approximately 85% of BZD overdoses also involved an opioid. Using the above data, it is reasonable to estimate an incidence of at least 0.183% for BZD and opioid overdoses in the general population. An estimated incidence for age cohort 40-49 years was 0.0097 events per person for males, 0.0132 events per person for females. This was based on data reported to the National Poison Data System. Total events to the American Association of Poison Control Centers were 1,213,110 for males and 1,264,405 for females. In the 40-49 year age group, 59,204 were male and 83,177 were female. Twenty percent of events were accounted for by sedatives and opioids. Using these data estimated events per person were calculated as follows: Male 11,841/1,213,100 and Female 16,635/1,264,405. Estimations were performed since there is a general lack of well described "denominator" data.

OVERALL INCIDENCE SUMMARY

INCIDENCE

mean 0.00105 and SD 8.672E-6

INCIDENCE SUMMARY

The Bayesian posterior distribution for the incidence rate given the active military analog data under an uninformative prior is Gamma(shape=14660.21, rate=13962101) with mean 0.00105 and SD 8.672E-6. Evidence Reference: Hesse E. Poisoning-related hospitalizations and risk factors for self-inflicted poisoning in the active component, U.S. Armed Forces, 2001-2010. MSMR. 2011 Nov;18(11):9-13. PMID: 22145849. Analog – active military. 14979 events with IR 105 per 100kpy. This translates to 14265714 person-years. IR: 1.05E-3 (95%CI: 1.033E-3, 1.067E-3).

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
0.00105

SD
8.672E-06

Gamma
(Shape): 14660.2
(Rate): 1.39621E+07

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Al-Tajir, et al. 2005	Terrestrial	1

Citation	Source	LOC Value
Barger, et al. 2014	Spaceflight	4
Beecher, 1944	Analog	2
Bronstein, et al. 2008	Terrestrial	1
Hesse, 2011	Analog	2
Saile, et al. 2017	Spaceflight	3
Putcha, et al. 1999	Spaceflight	2
Johnston, 2011	Spaceflight	2
Locke, 2011	Spaceflight	2

The Hesse 2011 study is the best available data for making our estimations as it is a 10 year surveillance study evaluating the incidence of overdose events in active military. The Barger study is a spaceflight study and therefore is small but shows no evidence of OD from BZD or opioid. An incidence rate of 2 events in 49.49 person years (0.04 events per person years) was determined based on anecdotal report of what appears to be a residual drowsiness after using BZD as a sleep-aid event (poster session Johnston, 2011) and extrapolation of incidence data (Saile, 2017). Per reports by Putcha (1999) and Locke (2011), incidence of side effects from medications used by astronauts were 15% and 12.5% , respectively. These data only report expected side effects of the medications not overdose events. There is a paucity of space epidemiologic data regarding medication overdoses. From previous CLiFFs, a report of 2 anecdotal cases of sleep aid medication were reported via Johnston, 2011. Search for this citation did not produce an article for cross reference. Putcha and Lock provide reasonable information of overall trend of adverse effects to medications, but not overdose incidence per se. Anecdotal report of 2 events of overdose of a sleep medication was noted by Johnston (2011), as noted in the previous CLiFF. The medication and dose was unidentified. One crew member had some difficulty awakening the following morning but did not require any treatment and woke up on their own. There was no mission impact. Given the lack of overall spaceflight data, this reference was included, though it is graded 2 due to lack of overall detail regarding the actual overdose and case. Putcha (1999) noted that over the course of 19 U.S. Space shuttle mission, in the 219 records obtained medications were primarily used for space motion sickness (47%) and sleep disturbances (45%) primarily. Of the medications used 85% of doses had no reported side effects, thus presumptively 15% did. Characteristics of these side effects were not clear. Given lack of detail this resource was rated 2. Locke (2011) describe similar trend data. Rate of side effects from sleep-related medications was noted at 12.5%. Additional detail, again, was unavailable. This resource was rated 2 as it provided useful trend data but additional breakdown of type of medication, symptoms, and duration effect. This evidence was similarly rated 2. The Headquarters of the Army (2012) in their heath-related strategic report, noted epidemiologic data pulled from department inquiries and surveys. Numbers for instances of substance abuse as well as death related to substance abuse, particularly as it relates to stress and mental health, were reported. While it provides a number of soldiers seen for overdose related incident, what fraction of total emergency room encounters this represented was not reported. The rate that was provided was a percentage deaths caused by overdose during death investigations. Given the presence of some epidemiologic data, but lack of “denominator” information, this resource was rated 2. Butler (2011) provides summary data from the FDA in 2007 regarding the number of adverse drug events related to oral transmucosal fentanyl often used for pain management in tactical combat casualty care. However, these event reports were not specific to the analogue population. Due to questionable relation to analogue population of the epidemiologic data provided this resource was rated 1. Beecher (1994) notes occurrences of adverse event in the use of intramuscular morphine in soldiers suffering from combat injuries, particularly in demanding environmental situations that altered overall pharmacokinetics of the medication that was used. No epidemiologic data was discussed since specific numbers could not be acquired. This resource was rate 1. Mowry (2015) is the annual summary report from 2014 from the American Association of Poison Control Center’s National Poison Data System. This database captures overdose events reported to poison control centers across the United States. Specific numbers regarding number of cases related to benzodiazepines or opioids, fraction of individuals receiving treatment, and general duration of action. On quick cross reference to the reports from 2019 numbers are similar. One limitation is that the epidemiologic percentages represent a fraction of people who have overdosed in general, and extrapolation of incidence as a fraction of the general population can not be directly generated. Given the availability of numbers and data to compute risk assumptions this resource was rated a 3. Rhyee (2014), is the annual summary report from 2014 from the Toxicology Investigators Consortium Case Registry. This database captures case reports of patients seen in a hospital or ambulatory setting by medical toxicologist. This source provided similar epidemiologic information to Mowry (2015). Additionally, it provides a more specific breakdown of treatment strategies. This resource was rated a 3. Martin (2015), is a systematic review that attempted to describe the prevalence of overdose in a more general population. It’s summary prevalence notes a fairly high (45.5%) rate of individuals that experience a non-fatal overdose at some point in their life. Notably, however, the studies acquired from their systematic review appear to primarily capture individuals who may suffer from substance use disorder, rather than a general overall terrestrial population, being that man of the individuals were noted to commonly use cocaine, methamphetamine, “tranquilizers,” “illicit substances,” and alcohol. This may limit its external validity. This resource was rated a 2.

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

60 minute pre-flight behavioral assessment of psychiatric and psychological fitness for launch. This is conducted as close to launch date as possible and intrinsically assesses risk factor for susceptibility to substance use and abuse such as stressful life events or history of emotional trauma.

BEST CASE SCENARIO DEFINITION

A benzodiazepine or opioid medication overdose that results in a respiratory perturbation but oxygen saturation that remains above 88%.

WORSE CASE SCENARIO DEFINITION

A benzodiazepine or opioid medication overdose that results in a respiratory perturbation causing an oxygen saturation to decrease below 88%.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

We estimate the best case probability to be 55.5% and worst case probability to be 44.5%. Rhyee 2015 reports that 6.7% of all reported overdoses were from BZD while 8.8% were related to opiates. Flumazenil was administered in 1.1% of all overdose cases (16.4% of benzodiazepine overdoses) while naloxone was administered in 5.8% of all overdose cases (65.9% of opiate overdose cases). From this information the total CLIFF relevant overdoses (opioids and benzodiazepines) stands at 15.5% of all overdoses reported in the study with reversal agents administered to 44.5% of these cases. This number is similar to the 52.8% of nonspecific overdose cases lasting longer than 8 hours reported in Mowry, 2015. However, since the Mowry, 2015 number is non-specific and includes overdoses that are not inclusive of opioid of BZD it is expected to be an overestimation so the 44.5% number was chosen to represent the worst case percentage.

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

Citation	Source	LOC Value
Rhyee, et al. 2015	Terrestrial	N/A
Mowry, et al. 2015	Terrestrial	2

Mowry, 2015, presents duration of effect data but does not specify type of overdose. In this study 52.8% of cases lasted more than 8 hours (Mowry, 2015). This is in line with the definition for this case but the lack of agent specificity makes this data of limited use. ToxIC data (Rhyee, 2015) reports agent specific and treatment data for patients seen by toxicologists in a hospital or ambulatory setting but stops short of treatment duration. Since neither study provides an answer on its' own a proxy of administered treatment from Rhyee, 2015 was used to define WC probability and face-value verified with the duration data from Mowry, 2015. Rhyee 2015 reports that 6.7% of all reported overdoses were from BZD while 8.8% were related to opiates. Flumazenil was administered in 1.1% of all overdose cases (16.4% of benzodiazepine overdoses) while naloxone was administered in 5.8% of all overdose cases (65.9% of opiate overdose cases). From this information the total CLIFF relevant overdoses (opioids and benzodiazepines) stands at 15.5% of all overdoses reported in the study with reversal agents administered to 44.5% of these cases. This number is similar to the 52.8% of nonspecific overdose cases lasting longer than 8 hours reported in Mowry, 2015. However, since the Mowry, 2015 number is non specific and includes non benzo/non opiate overdoses it is expected to be an overestimation so the 44.5% number was chosen to represent the WC percentage. One caveat is that the vast majority of toxicology cases (> 75 % according to Rhyee, 2015) are related to intentional abuse or intentional self harm. A further 7.1% are related to animal envenomations which are not applicable to spaceflight population. Drug abuse and suicidality may certainly arise de novo in any population but behavioral health conditions (specifically suicidality) are covered in separate CLIFFs and de novo drug abuse is less likely to be a significant factor for astronauts on mission given limited supplies, intensive psychological screening/support, and mission task requirements. With that said, there is little discussion of substance abuse in long duration space analogues beyond anecdotal reports of alcohol use (Newman, M, Schwartz, J Report Uncovers Astronauts' Heavy Alcohol Use, New York Times, 2007).

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: 0.00105 SD 8.672E-6	55 - 55	100	0.73	50	4	8	0	0	0	0	0
Treated Worst Case (TWC)		45 - 45	100	0.73	50	4	48	0	0	10	0	0
Untreated Best Case (UTBC)	N/A	N/A	N/A	0.73	50	4	8	0	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	0.73	100	8	48	100	0	0	20	80

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

Overdose of opioid or BZD are by definition medication-induced disruptions in normal physiology that, in the case of the astronaut population, would occur in otherwise healthy individuals. Treatment is supportive in the vast majority of cases, often consisting of monitoring respiration rate and oxygenation while the patient metabolizes the compound. For severe cases, both medications can suppress respiratory rates below the necessary threshold to sustain life. As long as respiratory rates can be maintained (either through external artificial respirations, repeated stimulation of the patient, or use of reversal agents, there are no long term consequences, and the patient will recover fully. Subsequent treatment focuses on addressing the causes of the overdose an focus on dose adjustments, occupational controls, and/or addiction counseling. For these reasons, if the overdose is recognized promptly, treatment is available, and it is administered correctly, survival is near enough 100% to be insignificant (Wermeling, 2015).

TREATED BEST CASE (TBC) SCENARIO COMMENTS

Note that by definition for this condition the best case scenario is a patient with a saturation that does not decrease below 88%. RTDC and LOCL are therefore expected to be 0% in the TBC scenarios.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

Both opioid and benzodiazepine overdoses are medication-induced disruptions in normal physiology that, in the case of the astronaut population, would occur in otherwise healthy individuals. Treatment is supportive in the vast majority of cases, often consisting of supporting respirations while reversal agents are administered or the patient metabolizes the compound. For severe cases, both BZDs and opioids can suppress respiratory rates below the necessary threshold to sustain life. As long as respiratory rates can be maintained (either through external artificial respirations, repeated stimulation of the patient, or use of reversal agents) there are no long term consequences, and the patient will recover fully. Subsequent treatment focuses on addressing the causes of the overdose and focus on dose adjustments, occupational controls, and/or addiction counseling. For these reasons, if the overdose is recognized promptly, treatment is available, and it is administered properly survival is near enough 100% to be insignificant (Wermeling, 2015). Worse case scenario as defined for this condition is a respiratory perturbation that drops below 88%. Christenson, 2000, noted that 49% of hospitalizations last longer than 4 hours. Clemency, 2019, similarly noted this proportion to be 69% in a population primarily treated with intranasal naloxone for opioid toxicity. They did not define the number of patients with saturation lower than 88% but we assume those needing treatment with naloxone met this criteria. With longer acting medications duration of symptoms may last longer, up to several days, as noted with methadone and symptoms detectable up to 48 hours (Zamani, 2020). As noted in the summary for the treated best case scenario, rates of anoxic brain injury are not well defined, and range between 0.80% to 9.8%. Acute mortality was 0.19% to 0.84%, based on fatality of all ingestions reported to the American Association of Poison Control Centers in the terrestrial populations.(Mowry, 2015) The minimum duration of observation and monitoring should be no shorter than 4 hours. The maximum duration was chosen based on the pharmacokinetics (terminal elimination phase concludes at 48 hours) and pharmacodynamics of valium (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/013263s094lbl.pdf). For this CLiFF, anoxic brain injury was used as the surrogate for RTDC. Oladunjoye, 2020, reported a prevalence of 0.8% for anoxic brain injury from opioid use. Marrow, 2019, reported a prevalence of 3% of encephalopathy, though this is not specifically defined as an anoxic or hypoxic injury. Mortality data is partially limited as most large surveillance reports encompass all ingestions or a fraction of overdoses in general and the data is clouded by inability of patients with signs of overdose to receive prompt treatment. If benzodiazepine and opioid overdoses are treated promptly and consecutively with sufficient doses of reversal agents in the absence of other disease processes (at which time morbidity and mortality would be attributed to the other pathologic process) the treated worst case scenario should result in 0% mortality.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

The best case scenario is unlikely to require treatment, therefore this would be the same duration as the treated best case scenario. With that said, RTDC and LOCL are expected to be 0% given the definition of the best case scenario.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

For UTWC the duration would be expected to be similar to TWCS given that the reversal agents are not curative and they have shorter half lives than the overdose-inducing agents. Thus our longest duration range will still map to the terminal elimination half life of diazepam. The CDC reported an age adjusted rate of drug overdose deaths per 100000 was 19.8 in 2016 (Hedegaard, 2017). The American Association of Poison Control Centers report and overall fatality rate in adults (from all ingestions) of 0.19%, of these 7.68% were attributed to sedative hypnotics or opioids (single agent exposures) (Mowry, 2015). The reason 20-80%% was chosen for LOCL in UWCS is that the pharmocokinetics of these drugs which can reverse overdose only function if the duration of hypoxemia is brief. Thus, if there is no treatment available promptly at the time the oxygen saturation decreases, then the patient may very high mortality (Gilhooley 2019). A patient with a saturation around 70% would have a lower mortality than one who dips to 40%, and these mortality differences we estimate to span from 80% at the lower levels of the saturation range and 20% mortality at the higher levels, closer to 88%. When compiling inventory for future long-duration space flight missions, this should be strongly taken into consideration to ensure appropriate stockpiles of these reversal medications.

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

Citation	Source	LOC Value
Christenson, 2000	Terrestrial	N/A
Clemency 2019	Terrestrial	
Zamani 2020	Terrestrial	
Gilhooley 2019	Terrestrial	

Christenson 2000, prospective inner city hospital. Shortest treatment duration 2 hours, longest >4 hours. Clemency same, <2 hours or >4 hours. Zamani 2020 longest identified duration of treatment was 48 hours. Given the pharmacokinetics of BZDs and opioids available in the CRT, we would expect peak effect to occur within 8 hours, therefore TBC and UBC would both be under 8 hours whereas TWC and UWC would never be longer than 48 hours (e.g. BZD overdose would not last longer than 48 hours and an untreated OD the patient would either have resolution of symptoms or be incapacitated).

Once saturations begin to decline, the probability of circulatory arrest is imminient as the survival plots are similar at baseline Sats of 90, 80, 70, and 60 in patients (Gilhooley 2019) - this data set consists of organ donor patients on life sustaining treatment, and in these cases terminal physiological deterioration lasted an average total of 14 min: 6 min of severe hypoxia, 4 min of hypotension with hypoxia, and a final terminal bradycardic, hypotensive, and hypoxic phase lasting 4 min. In our astronaut patient population this would likely be longer but unlikely to exceed 8 hours as noted in CP2 above.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Oldunjoye 2020	Terrestrial	N/A
Stevens 2017	Terrestrial	
Salzman 2020	Terrestrial	
Heyerdahl 2008	Terrestrial	
Belz 2006	Terrestrial	
Hesegawa 2014	Terrestrial	

Oladunjoye - Systematic review. Showed 0.8 % anoxic brain injury overall (9.8% in those with mech ventilation, 0.2% in non-requiring). Hasegawa 2014, 10% ED patients intubated for opioid overdose never came off vent. Stevens 2017 - 6 year retrospective - 8% icu admitted patients had anoxic brain injury. RTDC (surrogate being anoxic brain injury but not death) could be considered to be 0.2% sed on this terrestrial data but given pharmacokinetic data (Wermeling) the likelihood of experiencing anoxic brain injury if sufficient supplies are available is essentially 0%. This rationale is backed by the fact that most anoxic brain injury in non-spaceflight population is due to delay in supportive care. Data from retrospective review: Salzman data shows 13% of patients presenting to ED received naloxone. Heyerdahl similar at 14% for naloxone and 23% for flumazenil. Belz showed 48% had respiratory rate of <10 and 68% of cases received naloxone. These are not generalizable to the astronaut population because monitoring would be much more vigilant and any patient with obvious respiratory compromise would promptly receive reversal.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Morrow 2019	Terrestrial	N/A
Bohnert 2011	Terrestrial	
Garg 2017	Terrestrial	
Volkow 2019	Terrestrial	
Wermeling 2020	Terrestrial	
Hasegawa 2014	Terrestrial	

Morrow 2019, 7.3-9.1% mortality in ICU patients with opioid toxicity. Bohnert 2011, adult veterans 0.04% fatality rate for veterans who are prescribed opioids. Garg 2017, surveillance report of Medicaid patients - 4 year study of those Rxd an opioid. Volkow 2019 systematic review demonstrating opioid OD fatalities is 29.7-43.4 per 100,000. However, with appropriate resources, opioid overdose, which is the more commonly life-threatening condition, is 100% treatable and should result in zero chance of LOCL (Wermeling, 2020). Hasegawa mortality was 10% of ED patients with mixed overdose requiring intubation.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope Overview Best Case Definition: A benzodiazepine or opioid medication overdose that resolves within 8 hours and does not require treatment. Worst Case Definition: A benzodiazepine or opioid medication overdose that requires more than 8 hours to resolve and/or requires treatment. Essentially this is mistaken ingestion of pain medication that occurs secondary to use for another condition. This condition is typically more difficult to determine terrestrially because of the inability to quickly ascertain medication reconciliation. The treatment of this condition is primarily the management of the "ABCs." This condition is typically self-limited assuming that airway and breathing can be monitored and appropriately maintained. Diagnostic Scope and Resourcing In the best-case scenario, diagnosis is based on history, physical examination, and medication reconciliation. In the worst-case scenario, diagnosis is based on history, physical examination, and medication reconciliation. Clinical Phase 1 Duration and Rationale This version of IMPACT presumes physician level knowledge, skill, and ability will be present on the mission. The CRT working group SME consensus duration is as follows: CP1 BC (Treated or Untreated): 0.73 hours This is the longest reasonable time to complete this task for an experienced clinician adjusted for being in the spaceflight environment to do the following: 1 - Take a proper history of the patient 2 - Perform a physical on the patient CP1 WC (Treated or Untreated): 0.73 hours (this is the same as BC because the differential is the same and the determination of WC vs BC will be determined at the completion of CP1). This is the longest reasonable time to complete this task for an experienced clinician adjusted for being in the spaceflight environment to do the following: 1 - Take a proper history of the patient 2 - Perform a physical on the patient The highest scope of practice code used in this CRT which includes interpretation of diagnosis, performing diagnostic tests and performing treatment would be a four. Treatment Scope and Resourcing In the best-case scenario, treatment does not exist, which is the basis for the definition. The worst case scenario, where the patient is likely to result in pulmonary failure, monitoring of airway and breathing in the most critical step. Additionally, antidotes to therapy are also given to help the patient recover more quickly. Most overdoses in terrestrial populations (best or worst case) are resolved without medication but with potential need for ventilation support. We have NOT included ventilation support in this CRT as this would be part of a different condition (Respiratory Failure (ICL - 080) condition). The use of capnography helps determine if the condition is ICL 012 (this one) or ICL 80 (respiratory failure). Communications and Support Needs In the best-case and worst-case scenario, diagnosis and course of treatment is uncomplicated and likely within the scope of care of onboard crew members.

IMM CLIFF RECONCILATION COMMENTS

The best and worst case scenario definitions were unchanged. The calculated incidence, however, is reduced in the IMPACT CLiFF given analysis of differing literature in an analog population. The prior reference used in the IMM CLiFF was based on the spaceflight population but rather than an overdose, this source noted 2 instances of side effects from the medications. Given that those two instances appeared to be morning drowsiness after use of these medications as sleep aids without perturbation of respiratory effort (the main mechanism by which patients would be potentially at risk for morbidity or mortality from over administration of a BZD or opioid) this was not deemed a reference that actually referred to overdose events. Therefore, a new expected incidence rate was calculated based off the analog active military population, which was 0.00105 with a standard deviation of 8.672E-6. Even this low rate is a likely overestimate as we would expect the analog population to have slightly higher rates of this pathology than the astronaut population as they do not undergo the same rigorous psychological testing as individuals preparing for spaceflight.

LIMITATIONS SUMMARY

Limitation in the definition: Opioid overdose by our best case definition is not truly an overdose if it is self-limiting and does not require treatment. We may consider re-defining "best case scenario" definition in future iterations to be "respiratory perturbation that results in reduction in oxygen saturation no lower than 95%." In future algorithms, recommend that the worst case scenario also be defined as "respiratory perturbation that results in reduction in oxygen saturation below 88%" to reflect the increased danger of reductions in oxygen saturation below that important inflection point of the hemoglobin-oxygen dissociation curve. The current definition of episode lasting greater than 8 hours or requiring treatment is similarly difficult to distinguish from the treatment state of the patient and therefore complicates the computations for this CLiFF as the need for treatment is found in the definition, which creates a paradox with UBC and TBC and UWC and TWC. Regarding the realistic incidence of an UWC scenario transpiring in the highly regulated spaceflight environment, side effects from BZDs will likely be the most common issue encountered, rather than BZD overdose requiring reversal agent or of more than 8 hour duration. Opioid overdose in an opioid naive population is only likely in spaceflight in the presence of a unique pathologic process that is painful enough to require treatment with high dose opioids (e.g. perforated bowel). The data available is likely not representative of the true scenarios that will realistically unfold in spaceflight, but as our analysis reveals a very low calculated incidence, we feel it is sufficiently reflective of the low numbers that it is justified to maintain the calculations as they stand in order to have a foundation in prior published data points. Lastly, the likelihood of a crewmember even requiring opioid treatment would be mission-dependent in terms of the duration of the mission (e.g. longer mission would increase likelihood of new pathology arising), time/distance to RTDC and also the physical requirements of the mission (e.g. multiple EVAs will increase chance of MSK injury).

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)									0	3763	0	0
Untreated Best Case (UTBC)									0	3763	0	0
Treated Worst Case (TWC)									0	3763	0	0
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.

REFERENCES

Reference
Al-Tajir GK, Kelly WN. Epidemiology, comparative methods of detection, and preventability of adverse drug events. Ann Pharmacother 2005 Jul;39(7-8):1169-74.
American Medical Association. Central and Peripheral Nervous System. Guides to the Evaluation of Permanent Impairment. 6th ed. Chicago: American Medical Association Press; 2008. p. 321-45.
Bertini G, Russo L, Cricelli F, Daraio A, Giglioli C, Pini C, Poli C, Taddei T, Taiti A, Terni G, et al. Role of a prehospital medical system in reducing heroin-related deaths. Crit Care Med. 1992 Apr;20(4):493-8. doi: 10.1097/00003246-199204000-00011. PMID: 1559363.
Barger LK, Flynn-Evans EE, Kubey A, Walsh L, Ronda JM, Wang W, Wright KP Jr, Czeisler CA. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. Lancet Neurol. 2014 Sep;13(9):904-12. doi: 10.1016/S1474-4422(14)70122-X. Epub 2014 Aug 7. PMID: 25127232; PMCID: PMC4188436.
Beecher HK. “Delayed morphine poisoning in battle casualties” Journal of the American Medical Association 1944 124(17):1193-1194
Bronstein AC, Spyker DA, Cantilena LR, Jr., Green JL, Rumack BH, Giffin SL. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. Clin Toxicol (Phila) 2009 Dec;47(10):911-1084.
Butler Jr. F.K. “TCCC Update” Journal of Special Operations Medicine 2011 11:73-74
Camí J, Farré M. Drug addiction. N Engl J Med. 2003 Sep 4;349(10):975-86. doi: 10.1056/NEJMra023160. PMID: 12954747.
Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: the haemoglobin-oxygen dissociation curve. Breathe (Sheff). 2015;11(3):194-201. doi:10.1183/20734735.001415
Cooper J. Sedative-Hypnotic Toxicity . Tarabar A, editor. WebMD - Medscape Reference . 2009. New York, WebMD. 8-31-2011.
Garg RK, Fulton-Kehoe D, Franklin GM. Patterns of opioid use and risk of opioid overdose death among Medicaid patients. Med Care 2017;55(7):661–668
Goodman GP, DeZee KJ, Burks R, Waterman BR, Belmont PJ, Jr. Epidemiology of psychiatric disorders sustained by a U.S. Army brigade combat team during the Iraq War. Gen Hosp Psychiatry 2011 Jan;33(1):51-7.
Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013;13(2):214-223.
Hesse E. Poisoning-related hospitalizations and risk factors for self-inflicted poisoning in the active component, U.S. Armed Forces, 2001-2010. MSMR. 2011 Nov;18(11):9-13. PMID: 22145849.
Headquarters, D. o. t. A. (2012). Army 2020: Generating Health & Discipline In The Force Ahead Of The Strategic Reset. D. o. t. Army
Höjer J, Baehrendtz S, Gustafsson L. Benzodiazepine poisoning: experience of 702 admissions to an intensive care unit during a 14-year period. J Intern Med. 1989 Aug;226(2):117-22. doi: 10.1111/j.1365-2796.1989.tb01365.x. PMID: 2769176.
International Space Station Program. Medical Standards for ISS Crewmembers - MED Vol A. 3.2 ed. NASA; 2011.
Johnston S. Sleep medication. Kerstman E, editor. 2011. 9-2-2011.
Jones CM, McAninch JK, 2015. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am. J. Prev. Med 49, 493–501
Locke J. Survey of On-Orbit Sleep Quality (Sleep Quality Questionnaire) . 2011. 9-5-2011. Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. Arch Intern Med 2007 Sep 10;167(16):1752-9.
Mowry, J. B., et al. (2015). "2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report." Clin Toxicol (Phila) 53(10): 962-1147
NASA Mission Operations Directorate (MOD). International Space Station Integrated Medical Group Medical Checklist. Mission Operations Directorate (MOD), Systems Operations Data File (SODF) . 6-24-2011. Houston, TX, National Aeronautics and Space Administration (NASA).
National Collaborating Centre for Mental Health (UK). The Short-Term Physical and Psychological Management and Secondary Prevention of Self-Harm in Primary and Secondary Care. NICE Clinical Guidelines 2004;(16).
Putcha L, Berens KL, Marshburn TH, Ortega HJ, Billica RD. Pharmaceutical use by U.S. astronauts on space shuttle missions. Aviat Space Environ Med 1999 Jul;70(7):705-8.
Rhyee, S. H., et al. (2015). "The Toxicology Investigators Consortium Case Registry--the 2014 Experience." J Med Toxicol 11(4): 388-409.
Saile L, Boley L, Kerstman E. Integration RWS ISS STS Observed Incidence V2. 2017.
Shackelford SA, Fowler M, Schultz K, Summers A, Galvagno SM, Gross KR, Mabry RL, Bailey JA, Kotwal RS, Butler FK. Prehospital pain medication use by U.S. Forces in Afghanistan. Mil Med. 2015 Mar;180(3):304-9. doi: 10.7205/MILMED-D-14-00257. PMID: 25735021.
Shi SJ, Garcia KM, Meck JV. Temazepam, but not zolpidem, causes orthostatic hypotension in astronauts after spaceflight. J Cardiovasc Pharmacol. 2003 Jan;41(1):31-9. doi: 10.1097/00005344-200301000-00005. PMID: 12500019.

Reference

Stephens E. Toxicity, Opioids. Tarabar A, editor. WebMD - Medscape Reference . 2010. New York, WebMD. 8-31-2011.

Tansey WA, Wilson JM, Schaefer KE. Analysis of health data from 10 years of Polaris submarine patrols. Undersea Biomed Res 1979;6 Suppl:S217-S246.

Wedmore IS, Butler FK Jr. Battlefield Analgesia in Tactical Combat Casualty Care. Wilderness Environ Med. 2017 Jun;28(2S):S109-S116. doi: 10.1016/j.wem.2017.04.001. PMID: 28601204.

Weiss AJ, Elixhauser A, Barrett ML, Steiner CA, Bailey MK, O'Malley L. Opioid-related inpatient stays and emergency department visits by state, 2009–2014. HCUP Statistical Brief #219. Rockville, MD: Agency for Healthcare Research and Quality. 2016.

Wermeling DP. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Ther Adv Drug Saf. 2015 Feb;6(1):20-31.

White JM,

Irvine RJ. Mechanisms of fatal opioid overdose. Addiction. 1999 Jul;94(7):961-72. PMID: 10707430.

Hasegawa K , Brown DF , Tsugawa Y , et al . Epidemiology of emergency department visits for opioid overdose: a population-based study. Mayo Clin Proc 2014;89:462–71

Gilhooley, C., Burnhill, G., Gardiner, D., Vyas, H., & Davies, P. (2019). Oxygen saturation and haemodynamic changes prior to circulatory arrest: Implications for transplantation and resuscitation. Journal of the Intensive Care Society, 20(1), 27–33. https://doi.org/10.1177/1751143718764541

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