The following document contains data and analyses developed by the NASA Human Research Program Integrated Medical Model (IMM) v3.0, which has undergone rigorous testing and review within the NASA medical community per NASA Procedural Requirement 7150.2 and NASA Standard 7009, but still requires review by the external space flight medical community. Outstanding elements for review include: assessing the applicability of the IMM v3.0 outcomes, the relevance of stated assumptions, and clearly defining limitations. Given this, it is strongly recommended that care be taken when using the results of the simulation and the output should be weighted appropriately for its level of credibility with respect to informing any decision making. If you have questions regarding remaining review activities, please contact the IMM team. The scheduled release of IMM V4.0 in FY2017 follows completion of a full internal review against NASA standards as well as the successful external review from the appropriate medical and modeling communities.

EXECUTIVE SUMMARY

Assessing the medical risk associated with the lack of Advanced Life Support (ALS) Ventilation capability for the International Space Station (ISS) and Commercial Crew Vehicle (CCV). The approach taken to address this includes determining the crew health index (CHI), probability of evacuation (EVAC), and probability of loss of crew life (LOCL) of a 6 month design reference mission (DRM) with and without ALS Ventilation.

Although the Total number of Medical Events (TME) and CHI between the DRMs are similar, there is a significant difference in EVAC and LOCL between the DRMs with the EVAC and LOCL higher without ALS. The results are listed in Table 3. Regarding the influential conditions for EVAC, Tables 4 and 5 show the top 10 influential conditions with a comparison of conditions that require ALS. Regarding the influential conditions for LOCL, Tables 6 and 7 show the top 10 influential conditions with a comparison of conditions that require ALS. It is important to note that these results are conservative estimates of the impact of not manifesting ALS capability due to several of the IMM version 3 limitations and assumptions.

BACKGROUND

The Integrated Medical Model (IMM) simulates medical events during space flight missions and estimates the impact of these events on crew health. The IMM is a stochastic model that uses Monte Carlo methodology to simulate missions. The IMM consists of a three-step process:

1. Design Reference Mission (DRM) and crew member characteristics are specified
2. Medical events, treatment and outcomes for the DRM are randomly generated based on pre-defined probability distributions
3. Total crew health, medical, and required resource outcomes are summarized

METHODS

Crew and Mission Parameters

The DRMs including mission length, crew compliment, and number of Extravehicular Activity (EVA) events, were established in consultation with the requestor. Table 1 below shows the predefined crew profile information for this service request. The IMM standard ISS 6 month/6 crew profile was used.

The outcomes of certain IMM medical conditions are sex-specific and influenced by crew medical history. Pre-existing conditions that influence IMM outcomes include: coronary artery calcium score (CAC), dental crowns, contact lenses, and history of any prior abdominal surgery. Pre-existing conditions, as defined here, are consistent with historical U.S. crew data. The number of EVA excursions influences the probability of EVA-dependent medical conditions.

Table 1: Crew profile information for the DRMs.

	Sex	CAC	Crowns	Contacts	Prior Abdominal Surgery	EVA
Crew 1	male	yes	no	no	no	no
Crew 2	male	no	no	yes	no	yes(3)
Crew 3	male	yes	no	no	no	no
Crew 4	male	no	no	no	yes	no
Crew 5	male	no	no	no	no	yes(3)
Crew 6	female	no	yes	no	no	no

Medical Conditions and Resources

The incidence of IMM medical events occurring during simulated missions are based on historical mission and cohort data. For each condition, the percentage of “best case” and “worst case” scenarios are also specified, as well as a defined set of medical resources that is required to treat the medical condition. In-flight medical treatment is assumed to follow a specified protocol [5] for each medical condition and is constrained by resource availability on the ISS (*i.e.* the ISS medical capabilities (MedCap)). The one hundred medical conditions currently included in the IMM are shown in Appendix B.

In the current version of IMM, medical conditions are not treated unless all essential medical resources are available. Resources are classified as essential or non-essential, and as consumable or non-consumable. Consumable resources are decremented as required to treat medical events; if an item is essential, but has been depleted, then the given medical event will go untreated.

Table 2 provides a list of IMM medical conditions that require the Variable Oxygen System, VOS Intubated Patient Hardware (Ventilator/Respirator) or both.

Table 2. Medical Conditions Requiring the Variable Oxygen System and/or the VOS Intubated Patient Hardware (Ventilator/Respirator).

Medical Condition	Variable Oxygen System		VOS Intubated Patient Hardware (Ventilator/Respirator)	
	Best Case	Worst Case	Best Case	Worst Case
Acute Radiation Syndrome		X		
Altitude Sickness	X	X		X
Anaphylaxis		X		X
Angina/Myocardial Infarction		X		
Atrial Fibrillation/ Atrial Flutter		X		
Burns secondary to Fire		X		
Cardiogenic Shock secondary to Myocardial Infarction	X	X		X
Chest Injury		X		X
Choking/Obstructed Airway		X		X
Decompression Sickness Secondary to Extravehicular Activity		X		
Head Injury		X		X
Medication Overdose/Adverse Reaction		X		X
Neurogenic Shock	X	X		X
Seizures		X		
Sepsis		X		X
Smoke Inhalation		X		X
Stroke (cerebrovascular accident)		X		
Sudden Cardiac Arrest	X	X		X
Toxic Exposure (Ammonia)		X		X
Traumatic Hypovolemic Shock		X		X

Main Outcomes

The IMM primary medical outcomes include: total medical events (TME), crew health index (CHI), probability of evacuation (EVAC), probability of loss of crew life (LOCL), and required resources.

CHI is a calculated percentage using the quality-adjusted mission time lost (QAMTL) due to in-flight medical events and resources available to treat those conditions [3].

CHI = (1- (QAMTL ÷ Mission Length)) x 100

For a given condition, QAMTL is determined by summing the product of functional impairment and duration for all three clinical phases of that condition: i) diagnosis and initial treatment, ii) ongoing treatment, and iii) end-state. CHI percent values range from 0-100, where zero represents complete crew impairment and one hundred represents a completely functional crew.

EVAC in the context of IMM means that medical evacuation from the ISS would be considered for definitive treatment of the afflicted crew member(s). EVAC is considered an end state result if any of the following criteria is met: 1) potential LOCL; 2) potential significant permanent impairment; or 3) potential intractable pain. When EVAC is calculated by the IMM, no consideration has been given to the availability of a return vehicle or the likelihood of a successful clinical outcome should a return vehicle be available. EVAC was not part of the service request and is not reported below, although limitations relative to EVAC are briefly discussed in the Limitations section. This data is available on request.

LOCL in the context of IMM should be interpreted to mean that the clinical scenario resulted in death of the affected crew member(s). In the current version of the IMM, it is possible for crew members to be assigned more than one endstate of EVAC and/or LOCL. These assumptions should result in slightly high (conservative) IMM forecasts for the occurrence of EVAC and LOCL. Determining LOCL is the main objective of this service request.

Required resources for treatment are tracked for each DRM. The number of each resource that is needed from the given MedCap to treat all medical events is recorded. If more of any particular resource is used than is available in the given MedCap, then that is recorded as a “depleted” resource.

Modeling Approach

A 6 month ISS mission was simulated using IMM version three (v3). One hundred thousand (100,000) trials were run for each DRM, where each trial can be considered an individual "mission". This ensures that the distribution of outcomes meets convergence criteria. Convergence criteria are met when there is less than, or equal to a 5% change in the average standard deviation of the CHI, EVAC, and LOCL primary model outcomes in the last two - 1,000 mission increments.

IMM outcomes were determined for the "With ALS" DRM using the "All Treated" outcomes, because this is the most realistic scenario for the ISS given the resupply capability from earth and the availability of Russian medical resources. The "Without ALS" DRM uses the standard ISS MedCap where all conditions are treated until the essential resources of the ISS MedCap are depleted, after which point conditions go untreated.

To simulate the realistic scenario of resupply for the ISS for the "Without ALS" DRM, the VOS Intubated Patient Hardware (Ventilator/Respirator) and Variable Oxygen Systerm were given an initial quantity of zero while the other resources were given an initial quantity large enough to not be depleted over the length of the mission. TME and CHI are calculated as means, with 95% confidence intervals (CIs) for the associated distributions. EVAC and LOCL are probabilities, with 95% confidence intervals (CI) for EVAC and LOCL obtained using bootstrap resampling of the simulation output [3].

RELEVANT ASSUMPTIONS AND LIMITATIONS

1. The IMM is baselined to the ISS environment including medical capabilities.
2. All medical conditions are correctly diagnosed and all treatments are effective.
3. Conditions are treated in order of decreasing incidence and increasing crew member count (*i.e.* crew member one is treated before crew member two for any given condition) with Space Adaptation conditions treated first.
4. When there are insufficient *essential* medical resources to treat a condition, all available resources are consumed to reflect a partial treatment, but the medical condition is considered untreated.
5. All resources required to diagnose and treat a condition are consumed, even if treatment duration is greater than mission duration.
6. The IMM does not include a mission timeline, all conditions occur at launch on day one.
7. Medical conditions are independent of each other; i) a mission could end in more than one evacuation or loss of crew life being considered for the same crew member, and ii)

additional medical conditions can occur in a crew member assigned an end state of EVAC or LOCL.

8. IMM ISS MedCap do not take into account the availability of Russian medical resources, crew individual medical accessory kits, or the use of alternative medications for treatment.
9. IMM source data in the iMED database undergo regular updates to ensure best alignment to the real world system; this may affect the inclusion or exclusion of certain resources from the optimized MedCap, which would also effect resulting mass and volume.
10. Mass and volume for MedCap does not consider packaging materials.
11. Non-consumable resources are set to one in the All Treated scenario, regardless of ISS MedCap quantities.

RESULTS AND DISCUSSION

The specified DRMs were assessed using the IMM as described above in the Methods section above. One hundred thousand trials were simulated for each DRM with ISS MedCap to forecast IMM primary outcomes and resources required to treat each condition. Results are reported in Table 3.

Table 3. ISS 6 Month Outcomes With and Without ALS Capability.

	With ALS		With Out ALS	
	Mean/Probability	**95% CI**	**Mean/Probability**	**95% CI**
TME	104.87	86 – 125	104.88	86 – 125
CHI	93.53%	81.84 – 98.33	93.41%	81.02 – 98.32
EVAC*	0.0477	0.0463 – 0.0490	0.0551	0.0538 – 0.0566
LOCL*	0.0049	0.0044 – 0.0053	0.0161	0.0154 – 0.0169

** Probability of one or more events.*

There is no significant differences in TME or CHI between the two DRMs, as demonstrated by the overlapping confidence intervals. EVAC and LOCL are both statistically different between the “With” and “Without ALS” DRMs. EVAC rates are higher “Without ALS”. LOCL rates are an order of magnitude higher “Without ALS”. The much higher LOCL rate “Without ALS” results from more conditions that require ALS support being driven towards the untreated case. The top 10 conditions driving EVAC and LOCL for each DRM are shown in Tables 4 and 5 respectively, below.

Table 4. Top Ten Medical Condition Drivers of EVAC.

a) With ALS.

Rank	Scenario	Treated	Medical Condition	Percent Contribution	Cumulative Percent
1	WORST CASE	TREATED	VISUAL IMPAIRMENT AND/OR INCREASED INTRACRANIAL PRESSURE (VIIP)(SPACE ADAPTATION)	30.62	30.62
2	WORST CASE	TREATED	NEPHROLITHIASIS	10.50	41.12
3	WORST CASE	TREATED	DENTAL: ABSCESS	4.95	46.08
4	WORST CASE	TREATED	**SEPSIS**	4.73	50.81
5	WORST CASE	TREATED	**SMOKE INHALATION**	4.46	55.27
6	WORST CASE	TREATED	WRIST FRACTURE	3.22	58.49
7	WORST CASE	TREATED	**STROKE (CEREBROVASCULAR ACCIDENT)**	2.53	61.02
8	BEST CASE	TREATED	SMALL BOWEL OBSTRUCTION	2.20	63.22
9	WORST CASE	TREATED	HIP/PROXIMAL FEMUR FRACTURE	2.20	65.42
10	WORST CASE	TREATED	BACK SPRAIN/STRAIN	2.12	67.54

b) With Out ALS.

Rank	Scenario	Treated	Medical Condition	Percent Contribution	Cumulative Percent
1	WORST CASE	TREATED	VISUAL IMPAIRMENT AND/OR INCREASED INTRACRANIAL PRESSURE (VIIP)(SPACE ADAPTATION)	27.21	27.21
2	WORST CASE	UNTREATED	**SMOKE INHALATION**	13.41	40.61
3	WORST CASE	TREATED	NEPHROLITHIASIS	8.43	49.05
4	WORST CASE	UNTREATED	**SEPSIS**	4.66	53.71
5	WORST CASE	TREATED	DENTAL ABSCESS	4.38	58.08
6	WORST CASE	UNTREATED	**CHOKING/OBSTRUCTED AIRWAY**	2.66	60.74
7	WORST CASE	TREATED	WRIST FRACTURE	2.58	63.32
8	BEST CASE	TREATED	SMALL BOWEL OBSTRUCTION	1.75	65.07
9	WORST CASE	TREATED	HIP/PROXIMAL FEMUR FRACTURE	1.71	66.78
10	WORST CASE	TREATED	BACK SPRAIN/STRAIN	1.68	68.45

Table 5. Medical Conditions Requiring ALS: EVAC Influential Condition Rank Comparison.

Medical Condtion	Rank with ALS	Rank without ALS
Sepsis	4	4
Smoke Inhalation	5	2
Stroke (Cerebrovascular Accident)	7	unranked
Choking / Obstructed Airway	unranked	6

** The medical conditions are all worst case.*

In Table 4a, the conditions that require ALS ventilation, worst case Sepsis, Smoke Inhalation, and Stroke (Cerebrovascular Accident), are in bold typeface. They are the 4th, 5th, and 7th ranked influential conditions for EVAC in the DRM with available ALS. In Table 4b, the conditions that require ALS ventilation, worst case Sepsis, Smoke Inhalation, and Choking / Obstructed Airway, are in bold typeface. They are the 2nd, 4th, and 6th ranked influential conditions for EVAC in the DRM without available ALS. Table 5 illustrates the change in rank of the influential conditions for EVAC with and without ALS.

Table 6. Top Ten Medical Condition Drivers of LOCL.

a) With ALS

Rank	Scenario	Treated	Medical Condition	Percent Contribution	Cumulative Percent
1	WORST CASE	TREATED	**SEPSIS**	22.00	22.00
2	WORST CASE	TREATED	**TRAUMATIC HYPOVOLEMIC SHOCK**	16.50	38.49
3	WORST CASE	TREATED	**MEDICATION OVERDOSE/ADVERSE REACTION**	13.24	51.73
4	WORST CASE	TREATED	**STROKE (CEREBROVASCULAR ACCIDENT)**	11.61	63.34
5	WORST CASE	TREATED	**SMOKE INHALATION**	7.54	70.88
6	WORST CASE	TREATED	**HEAD INJURY**	6.31	77.19
7	WORST CASE	TREATED	**TOXIC EXPOSURE (AMMONIA)**	5.70	82.89
8	WORST CASE	TREATED	**CHEST INJURY**	4.89	87.78
9	WORST CASE	TREATED	APPENDICITIS	3.87	91.65
10	WORST CASE	TREATED	ABDOMINAL INJURY	2.65	94.30

b) With Out ALS

Rank	Scenario	Treated	Medical Condition	Percent Contribution	Cumulative Percent
1	WORST CASE	UNTREATED	**SMOKE INHALATION**	46.74	46.74
2	WORST CASE	UNTREATED	**SEPSIS**	16.24	62.98
3	WORST CASE	UNTREATED	**HEAD INJURY**	5.41	68.39
4	WORST CASE	UNTREATED	**STROKE (CEREBROVASCULAR ACCIDENT)**	5.29	73.68
5	WORST CASE	UNTREATED	**TRAUMATIC HYPOVOLEMIC SHOCK**	5.17	78.84
6	WORST CASE	UNTREATED	**CHOKING/OBSTRUCTED AIRWAY**	4.31	83.15
7	WORST CASE	UNTREATED	**TOXIC EXPOSURE (AMMONIA)**	3.94	87.08
8	WORST CASE	UNTREATED	**CHEST INJURY**	3.75	90.84
9	WORST CASE	UNTREATED	**MEDICATION OVERDOSE/ADVERSE REACTION**	2.95	93.79
10	WORST CASE	TREATED	APPENDICITIS	2.15	95.94

In Table 6a, the conditions that require ALS ventilation, worst case Sepsis, Traumatic hypovolemic shock, Medication Overdose/Adverse Reaction, Stroke (Cerebrovascular Accident), Smoke Inhalation, Head Injury, Toxic Exposure: Ammonia, and Chest injury, are in

bold typeface. They are the top 8 ranked influential conditions respectively for LOCL in the DRM with available ALS. In Table 6b, the conditions that require ALS ventilation, worst case Smoke Inhalation, Sepsis, Head Injury, Stroke (Cerebrovascular Accident), Traumatic Hypovolemic Shock, Choking/Obstructed Airway,Toxic Exposure (Ammonia), Chest Injury,Medication Overdose/Adverse Reaction, are in bold typeface. They are the top 9 ranked influential conditions respectively for LOCL in the DRM without available ALS. Table 7 illustrates the change in rank of the influential conditions for LOCL with and without ALS.

Table 7. Medical Conditions Requiring ALS: LOCL Influential Condition Rank Comparison.

Medical Condtion	Rank with ALS	Rank without ALS
SEPSIS	1	2
TRAUMATIC HYPOVOLEMIC SHOCK	2	5
MEDICATION OVERDOSE/ADVERSE REACTION	3	9
STROKE (CEREBROVASCULAR ACCIDENT)	4	4
SMOKE INHALATION	5	1
HEAD INJURY	6	3
TOXIC EXPOSURE (AMMONIA)	7	7
CHEST INJURY	8	8
CHOKING/OBSTRUCTED AIRWAY	unranked	6

** The medical conditions are all worst case.*

SUMMARY

Although the TME and CHI between the DRMs are similar, there is a significant difference in EVAC and LOCL between the DRMs with the EVAC and LOCL higher without ALS. The results are listed in Table 3. Regarding the influential conditions for EVAC, Tables 4 and 5 show the top 10 influential conditions with a comparison of conditions that require ALS. Regarding the influential conditions for LOCL, Tables 6 and 7 show the top 10 influential conditions with a comparison of conditions that require ALS. It is important to note that these results are conservative estimates of the impact of not manifesting ALS capability due to several of the IMM version 3 limitations and assumptions.

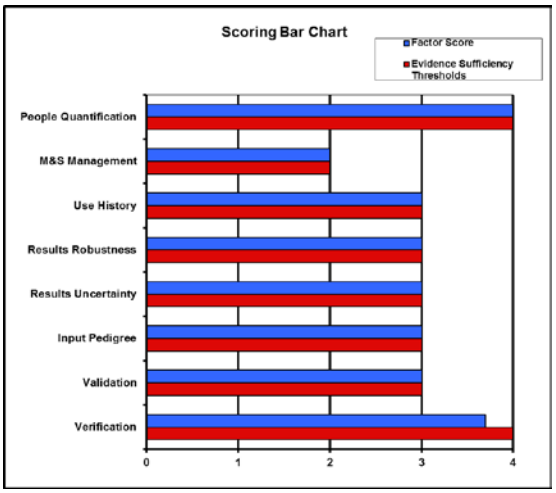
REFERENCES

1. Integrated Medical Model Project. Integrated Medical Model Operations Plan. JSC-66114. 2011. Houston, TX, NASA, Johnson Space Center, (document update in progress).
2. Integrated Medical Model Project. Integrated Medical Model Functional Requirements Document. JSC-66110. 2011. Houston, Texas, NASA, Johnson Space Center, (document update in progress).
3. Integrated Medical Model Project. Integrated Medical Model v3 Technical Description Report. JSC-66118. 2015. Houston, TX, NASA JSC, (document update in progress).
4. NASA technical standard for models and simulations 7009 (NASA STD 7009). 1-58. 7-11-2008 (reapproved 7-10-2013). Washington D.C., NASA.
5. ISS Medical Checklist (Med CL), 04 June 2014, NASA Johnson Space Center, Medical Operations Group.

APPENDIX A – IMM STATUS AT TIME OF SERVICE REQUEST REPORT

Validation status for IMM

IMM V&V Matrix: The following bar chart shows the IMM v3.0 MATLAB status of internal (black bars) and external (gray bars) IMM validation for each IMM element listed.



Compliance with NASA-Standard-7009 requirements

IMM Compliance Matrix: The IMM has no waivers to any of the requirements in the NASA-Standard-7009 for Models and Simulations (6); however there are certain requirements that are not applicable to the IMM and other requirements where IMM compliance has not yet been fully attained.

Compliant	Compliance Incomplete	Not applicable
27	20	2

Current NASA-Standard-7009 credibility assessment score

IMM Credibility Matrix: The following table shows the overall IMM v3.0 MATLAB credibility assessment score (CAS), individual factor CAS, customer-specified sufficiency thresholds, and weighted scores. Legend depicts CAS score designated range and color assignments from NASA-Standard-7009.

Factor	Sufficiency Thresholds	Factor Score	Weighted Scores	Overall Score
Verification	**4**	**3.7**	0.28	
Validation	**3**	**3**	0.45	
Input Pedigree	**3**	**3**	0.53	
Results Uncertainty	**3**	**3**	0.60	**3.06**
Results Robustness	**3**	**3**	0.45	
Use History	**3**	**3**	0.45	
M&S Management	**2**	**2**	0.10	
People Qualification	**4**	**4**	0.20	

Legend from NASA-STD-7009	
	CAS Score > Threshold ***Exceeds credibility requirements***
	Threshold ≥ CAS Score ≥ (Threshold-0.5) ***Ready for use***
	Threshold-0.5 > CAS Score ≥ Threshold-1.0 ***Use with caution***
	CAS Score < Threshold - 1.0 ***Use not recommended or to be used with EXTREME CAUTION by subject matter experts only***

Additional verification and validation information applicable to this analysis

None

Integrated Medical Evidence Database (iMED) code version and date accessed

iMED Lockdown ID: (22), created on (11/15/2016), iMED Lockdown ID: (25), created on (2/13/2016)

IMM version and code version

Data analysis for this report was generated using IMM v3.0 with release 2014a of MATLAB software. MATLAB and all other MathWorks product or service names are registered trademarks or trademarks of MathWorks, Natick, MA, USA.

Modifications made to the code for analysis

None

APPENDIX B: LIST OF THE CURRENT 100 MEDICAL CONDITIONS USED IN THE IMM.

ENVIRONMENTAL
Acute Radiation Syndrome
Altitude Sickness
Barotrauma (ear/sinus block)
Burns secondary to Fire
Decompression Sickness Secondary to EVA
Eye Chemical Burn
Headache (CO_2 induced)
Smoke Inhalation
Toxic Exposure: Ammonia
INJURY/TRAUMA
Abdominal Injury
Acute Compartment Syndrome
Ankle Sprain/Strain
Back Sprain/Strain
Chest Injury
Dental: Avulsion (tooth loss)
Elbow Dislocation
Elbow Sprain/Strain
Eye Irritation/Abrasion
Eye Penetration (foreign body)
Finger Dislocation
Fingernail Delamination Secondary to EVA
Head Injury
Hip Sprain/Strain
Hip/Proximal Femur Fracture
Knee Sprain/Strain
Lower Extremity (LE) Stress Fracture
Lumbar Spine Fracture
Neck Sprain/Strain
Neurogenic Shock
Paresthesias Secondary to EVA
Shoulder Dislocation
Shoulder Sprain/Strain
Skin Abrasion
Skin Laceration
Traumatic Hypovolemic Shock
Wrist Fracture
Wrist Sprain/Strain
MEDICAL ILLNESS
Abdominal Wall Hernia
Abnormal Uterine Bleeding
Acute Angle-Closure Glaucoma
Acute Arthritis
Acute Cholecystitis/Biliary Colic
Acute Diverticulitis
Acute Pancreatitis
Acute Prostatitis
Acute Sinusitis
Allergic Reaction (mild to moderate)
Anaphylaxis
Angina/Myocardial Infarction

MEDICAL ILLNESS (continued)
Anxiety
Appendicitis
Atrial Fibrillation/Atrial Flutter
Back Pain (space adaptation)
Behavioral Emergency
Cardiogenic Shock Secondary to Myocardial infarction
Choking/Obstructed Airway
Constipation (space adaptation)
Dental: Exposed Pulp
Dental Caries
Dental: Abscess
Dental: Crown Loss
Dental: Filling Loss
Depression
Diarrhea
Eye Corneal Ulcer
Eye Infection
Gastroenteritis
Headache (Late)
Headache (space adaptation)
Hearing Loss
Hemorrhoids
Herpes Zoster Reactivation (shingles)
Hypertension
Indigestion
Influenza
Insomnia (space adaptation)
Medication Overdose/Adverse Reaction
Mouth Ulcer
Nasal Congestion (space adaptation)
Nephrolithiasis
Nose bleed (space adaptation)
Otitis Externa
Otitis Media
Pharyngitis
Respiratory Infection
Retinal Detachment
Seizures
Sepsis
Skin Infection
Skin Rash
Sleep Disorder
Small Bowel Obstruction
Space Motion Sickness (space adaptation)
Stroke (Cerebrovascular Accident)
Sudden Cardiac Arrest
Urinary Incontinence (space adaption)
Urinary Retention (space adaptation)
Urinary Tract Infection
Vaginal Yeast Infection
Visual Impairment and Increased Intracranial Pressure (VIIIP) (space adaptation)