Clinical Finding Form (CliFF)

Branch Baseline

ICL10_Atrial Fibrillation/Atrial Flutter

Atrial fibrillation (A-Fib) is an irregular rhythm of the heart due to irregular contractility of the atria (out of sync with the ventricles). Symptoms can include palpitations, dizziness, shortness of breath, and weakness. (Mayo Clinic, NHLBI/NIH) There are four primary classifications of A-Fib: 1) Paroxysmal – a brief episode lasting 24 hours to 1 week in duration. 2) Persistent – an episode lasting longer than a week (but may resolve spontaneously). 3) Long-term persistent – An episode lasting more than a year. 4) Permanent – A-Fib that persists despite treatment. (NHLBI/NIH) Although terrestrially, A-Fib often presents with a rapid heart rate (Mayo Clinic), in astronauts it is often within a normal range. This is felt to be secondary to increased vagal tone in crewmembers due to their high level of physical fitness. (Barr, 2010). This may explain why most crewmembers diagnosed with A-Fib are found incidentally (Barr, 2010). Atrial fibrillation increases the risk of blood clot formation in the atria, thereby increasing the risk of ischemic cerebrovascular accident (Mayo Clinic). Treatment can include medications for rate control, anticoagulation, cardioversion, or ablation. In rare cases associated with bradycardia, pace making is required. (NHLBI/NIH) Atrial flutter is also caused by an abnormal rhythm of the atria, but it is regular and rapid. It also carries a risk of blood clot formation, increasing the risk of ischemic CVA. (Mayo Clinic)

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 have been no documented cases of Atrial Fibrillation or Atrial Flutter in U.S. Spaceflight. However, there have been cases (primarily of A-Fib) among active and retired crewmembers terrestrially. Lee et al, 2021 represents LSAH data from the HSRB Cardiovascular Risk Update CR SA-03267 approved May 13, 2021. It reports 9 cases of A-Fib/A-Flutter over 4359 person-years for active crewmembers (a total of 315 active crewmembers). An additional source providing information for the astronaut cohort is the NASA Atrial Arrythmia Summit Report reports a history of 11 cases of A-Fib/A-Flutter or SVT in active astronauts between 1959 and January 22, 2010. An additional 6 cases were reported in retired astronauts during the same time frame. There were reportedly 317 active and retired astronauts during this timeframe. Of the 23 cases, 22 occurred in men. The summit reports that between 2001 and 2010, five astronauts out of a cohort of approximately 100 in the active astronaut corps underwent radiofrequency ablation treatment for atrial arrhythmias (mostly atrial fibrillation). It should be noted that any long duration flyers found to have A-Fib were treated with ablation during this time period. (Barr, 2010) The LSAH data from the 2021 HSRB Cardiovascular update (Lee et al, 2021) will be used to inform the incidence for this CLiFF as it is felt to have several advantages over Barr, 2021. First, Lee et al, 2021 includes only active astronauts, whereas Barr, 2010 includes retired astronauts. The incidence of A-Fib/A-Flutter increase with age, so restricting to active astronauts is anticipated to provide a more accurate estimate of incidence. Second, Lee et al, 2021 includes only cases of A-Fib/A-Flutter whereas Barr, 2010 also includes supraventricular tachycardia.

ANALOG LITERATURE

These data were not used to inform the incidence distribution for this CLiFF. Hunter et al, 2013, is a retrospective 5 year study of UK Royal Air Force members from 2006-2011. 360 military aircrew were identified during this period. Of these, 23 were diagnosed with Atrial Fibrillation (primarily paroxysmal). The median age of those with a diagnosis of Atrial Fibrillation was 42 years old (range, 18-64 years old). Notably, 22 of the 23 aircrew diagnosed were men. Of the 23 crewmember who were diagnosed with Atrial Fibrillation during the study period, 8 required at least one of the following interventions: cardioversion, ablation, or pacemaker placement.

TERRESTRIAL LITERATURE

These data were not used to inform the incidence distribution for this CLiFF. Haim et al, 2015 is a prospective cohort study from 2004-2011 of prevalence and incidence of atrial fibrillation in an Israeli population of adults 20 years of age and older. Co-morbidities were not removed from data. New onset A-Fib incidence was stratified by gender and age. The incidence (per 10,000 person year at risk) of A-Fib was 635 in men as compared with 575 in women. The incidence was significantly higher among men at any age group and it increased from 47.7 at age <35 to 4427.6 in men >85 years of age and from 36.7 at age <35 to 3790 in women >85 years of age. Bjorck et al, 2013 conducted a retrospective period prevalence study in Sweden of adults 20 years and older. Co-morbidities were not removed from data. Incidence was not calculated.

OVERALL INCIDENCE SUMMARY

INCIDENCE

Mean: 0.00207
SD: 7.019E-4

INCIDENCE SUMMARY

Lee et al, 2021 (LSAH data from the HSRB Cardiovascular Risk Update CR SA-03267 approved May 13, 2021) was used to inform the incidence distribution for this CLiFF. It reports 9 cases of A-Fib/A-Flutter over 4359 person-years for active crewmembers (a total of 315 active crewmembers). The Bayesian posterior distribution for the incidence rate given the Active Astronaut data (9 events over 4359 person-years) is Gamma(shape=8.697, rate=4201.65) with mean 0.00207 and SD 7.019E-4.

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
0.0020699

SD
0.000701883

Gamma
(Shape): 8.697
(Rate): 4201.65

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Lee et al, 2021	Spaceflight	4
Barr, 2010	Spaceflight	4
Hunter et al, 2013	Analog	3
Haim et al, 2015	Terrestrial	1
Bjorck et al, 2013	Terrestrial	0

Lee et al, 2021 represents LSAH data from the HSRB Cardiovascular Risk Update CR SA-03267 approved May 13, 2021. It reports 9 cases of A-Fib/A-Flutter over 4359 person-years for active crewmembers (a total of 315 active crewmembers). Barr, 2010 is the NASA Atrial Arrythmia Summit Report. It reports a history of 11 cases of A-Fib/A-Flutter or SVT active astronauts between 1959 and January 22, 2010. An additional 6 cases were reported in retired astronauts during the same time frame. Hunter et al, 2013, is a retrospective 5 year study of UK Royal Air Force members from 2006-2011. 360 military aircrew were identified during this period. Of these, 23 were diagnosed with Atrial Fibrillation (primarily paroxysmal). The median age of those with a diagnosis of Atrial Fibrillation was 42 years old (range, 18-64 years old). Haim et al, 2015 is a prospective cohort study from 2004-2011 of prevalence and incidence of atrial fibrillation in an Israeli population of adults 20 years of age and older. Co-morbidities were not

removed from data. New onset A-Fib incidence was stratified by gender and age. Bjorck et al, 2013 conducted a retrospective period prevalence study in Sweden of adults 20 years and older. Co-morbidities were not removed from data. Incidence was not calculated.

CREWMEMBER SELECTION/PREVENTION

DISQUALIFYING CONDITIONS

Refer to Medical Evaluation Documents (MED) Volume A, Medical Standards for ISS Crewmembers, International Space Station Program, Rev 3.4 (2016).

PREFLIGHT PREVENTATIVE MEASURES

All mission assigned crewmembers for mission durations of 30 days or more are required to undergo the following monitoring: • 24-hour Holter Monitoring at L-365 days and as clinically indicated. (NASA, MedB 1.7) • Exercise treadmill testing at L-180 days and L-30/45 days (NASA, MR006L). • Pre- and Post-Flight resting ECG at L-9/6 months to L-10 days and R+0/3 days (NASA, MedB 1.6). • Heart-rate monitoring for 2 weeks during exercise training at L-1year, L-45 to L-15 days. In-flight heart-rate monitoring occurs during the first 2 weeks of every mission during every treadmill and cycle ergometer session, as well as during periodic fitness evaluation (PFE) sessions. Thereafter, inflight heart rate monitoring occurs during each (PFE), while exercising on the Russian cycle ergometer, or during contingencies. (NASA, MR019L)

BEST CASE SCENARIO DEFINITION

Atrial fibrillation or flutter that does not require emergent cardioversion, rate/rhythm control, or thromboembolic prophylaxis.

WORSE CASE SCENARIO DEFINITION

Atrial fibrillation or flutter that requires emergent cardioversion, rate/rhythm control, or thromboembolic prophylaxis.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

The worst-case scenario was informed by Hunter et al, 2013, a retrospective 5 year study of UK Royal Air Force pilots from 2006-2011. Of 28 aircrew who were diagnosed with Atrial Fibrillation during the study period, 8 required at least one of the following interventions: cardioversion, ablation, or pacemaker placement. This was considered a reasonable surrogate for the worst-case scenario and the population was felt to be a better analog for the Astronaut Corps than all-comer terrestrial data. Therefore, a worst-case probability of 37.48% and a best-case probability of 62.52% were assigned.

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

Citation	Source	LOC Value
Hunter et al, 2013	Analog	3

Hunter et al, 2013, is a retrospective 5 year study of UK Royal Air Force members from 2006-2011. 360 aircrew were identified during this period. Of these, 23 were diagnosed with Atrial Fibrillation (primarily paroxysmal). Of the 23 crewmember who were diagnosed with Atrial Fibrillation during the study period, 8 required at least one of the following interventions: cardioversion, ablation, or pacemaker placement.

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: 0.00207 SD: 7.019E-4	62.52 - 62.52	100	2.26	0	0.1	30.4	0	0	0	0	1.6
Treated Worst Case (TWC)		37.48 - 37.48	100	2.43	27.4116	0.3	127	5.60723	10	59	0	7.09
Untreated Best Case (UTBC)	N/A	N/A	N/A	2.26	9.11507	0.1	30.4	9.11507	0	0	0	1.6
Untreated Worst Case (UTWC)	N/A	N/A	N/A	2.43	100	0.3	127	100	10	59	0	10.18

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

The RTDC surrogate used was need for emergent cardioversion. Class I AHA/ACA recommendations for pharmacologic and electrical cardioversion of A-Fib include: 1) Patient's with A-Fib with rapid ventricular response and ECG evidence of acute MI or symptomatic hypotension, angina, or heart failure that doesn't respond promptly to pharmacologic measures, 2) Hemodynamic instability (Fuster et al, 2006). It was assumed that best-case scenarios would not have sequalae requiring emergent cardioversion. For worst-case scenarios, the need for emergent cardioversion was based studies indicating the proportion of A-Fib cases that are "unstable" (Tischler et al, 1990; Kanji et al, 2012). The RTDC probabilities for the worst-case scenario may be an overestimate because participants in these studies had multiple comorbidities (including cardiac comorbidities), and Kanji et al, 2012 specifically looked at ICU patients (who may be hemodynamically unstable based on other underlying illness/causes). Durations for the best-case scenarios are based on paroxysmal A-Fib. Durations for the worst-case scenarios are based on recurrent A-Fib (Go et al, 2018). The LOCL probabilities are based on age-restricted data for decades of life 30s-50s in untreated patients with A-Fib, using thromboembolic event as a surrogate for mortality (Lip et al, 2010).

TREATED BEST CASE (TBC) SCENARIO COMMENTS

The durations used were informed by Go et al, 2018 and relate to the duration of paroxysmal A-Fib episodes seen in the study population. This was a 5 year study of 1,965 adult participants with paroxysmal A-Fib. Notably, the mean age was 69 years old. 45% of participants were women. The median CHA2DS2-VASc score of participants was 3. Participants wore a holter monitor for 14 days. All participants were untreated. The minimum and maximum durations of runs of paroxysmal A-Fib from this study were assigned for this scenario: 0.1 hours (6 minutes) and 30.4 hours (1824 minutes). Class I AHA/ACA recommendations for electrical cardioversion of A-Fib include: 1) When A-Fib with rapid ventricular response does not respond to pharmacologic cardioversion with ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure, 2) Hemodynamic instability, 3) When the symptoms are unacceptable to the patient (Fuster et al, 2006). In a best-case scenario episode of A-Fib, these sequelae are not anticipated. Thus, the need for emergent cardioversion (the chosen RTDC surrogate) would not exist. Therefore, the RTDC probability for best-case scenarios was assigned 0%. Per Barr, 2010 most astronauts have a CHADS2 score of 0-1. When the score is expanded to CHADS2-VASC, sex is also included. Accounting for sex, astronauts could have scores from 0-2. (Points being collected for being female and having hypertension). Lip et al, 2010, a prospective cohort study of A-Fib (from the EURO Heart Study) included patients without mitral stenosis, previous valvular surgeries, and not on anticoagulation. There were 0, 162 (0.6%), and 184 (1.6%) thromboembolic events in participants with CHADS2-Vasc scores of 0, 1, and 2 respectively. Thus, using thromboembolic events as a surrogate for mortality, the LOCL probability was assigned a range of 0-1.6%.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

The durations used were informed by Go et al, 2018 and relate to the total duration of multiple A-Fib episodes seen in the study population. This was a 5 year study of 1,965 adult participants with paroxysmal A-Fib. Notably, the mean age was 69 years old. 45% of participants were women. The median CHA2DS2-VASc score of participants was 3. Participants wore a holter monitor for 14 days. All participants were untreated. The minimum and maximum durations were assigned as 0.2 hours and 120 hours, respectively. Class I AHA/ACA recommendations for electrical cardioversion of A-Fib include: 1) When A-Fib with rapid ventricular response does not respond to pharmacologic cardioversion with ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure, 2) Hemodynamic instability, 3) When the symptoms are unacceptable to the patient (Fuster et al, 2006). The minimum RTDC probability of 10% was informed by Kanji et al, 2012. In this retrospective observational study, consecutive patients admitted to either medical or surgical adult ICUs in 3 Canadian hospitals between Jan 1 and Dec 31, 2006 were considered. 325 patients were identified as having A-Fib during their ICU stay, and of these, 139 cases were determined to be new-onset A-Fib. Hemodynamic instability developed in 10% of patients with new-onset A-Fib. The mean age of participants with new-onset A-Fib was 71.6 years and 60% of participants were male. Notably, the admitting diagnosis was A-Fib in only 6 patients. Otherwise, admitting diagnoses included (sepsis, respiratory failure/pneumonia, cardiogenic shock/cardiac arrest, CVA, post-operative care, and "other"). There were notably many comorbidities (e.g. smoking, asthma, COPD on oxygen, valvular heart disease, HTN, CHF, cardiomyopathy, CKD, history of CVA, and diabetes). 39% of patients with new-onset A-Fib were on either a beta blocker, calcium channel blocker, or digoxin prior to admission. The maximum RTDC probability of 59% was informed by Tischler et al, 1990 a retrospective review conducted at Brigham and Women's Hospital from Jan 1, 1985-Dec 31, 1988. 87 patients met the inclusion criteria of presumed new-onset A-Fib (symptoms less than 48 hours), and technically adequate echocardiograms performed while in sinus rhythm during the hospitalization. Mitral stenosis was excluded. Participants were classified as "unstable" if they met any of the following criteria: hypotension (SBP < 90mmHg), angina or chest pain with ST-segment depressions of at least 1 mm in at least 2 leads, congestive heart failure based on physical exam and x-ray, or witness syncopal episode. 59% of patients were considered unstable in this cohort. Notably, the average age of participants was 61 years for stable A-Fib patients, 66 years for unstable A-Fib patients. The study included nearly 50% female participants. Significant co-morbidities existed in the cohort. Despite the presumption of new-onset A-Fib, pre-existing A-Fib was documented in 31% of unstable patients. Other comorbidities included valvular issues (aortic stenosis /regurgitation, mitral regurgitation), hypertension, angina/MI, COPD. The probability of LOCL was assigned 0-7.09% based on all-cause mortality data presented in Lee et al, 2018 a retrospective cohort study of 15,411 patients with A-Fib, identified by ICD-10 code from a national database in South Korea between 2002-2013. The range of all-cause mortality for this group spans from 0-10.18%, but this value was discounted by 32.3% based on data in the study showing decreased mortality of 32.3% for those on anticoagulation therapy. Notably, only a third of the patients in this cohort were less than 60 years old. However, all-cause mortality was provided by decade of life, so the maximum probability value was derived by age restricting the data to decades 20s-50s (464 deaths in 4556 patients) and then discounting as above to account for the benefit of anticoagulation therapy. While valvular AF was excluded from this study, pre-existing co-morbidities of ischemic heart disease, prior myocardial infarction, and congestive heart failure existed in the patient population, which indicates that this may be an overestimate of LOCL probability.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

The same values were used for duration, RTDC probability, and LOCL probability for this scenario as the treated best-case scenario. The following

explanation is identical to the treated best-case scenario. The durations used were informed by Go et al, 2018 and relate to the duration of paroxysmal A-Fib episodes seen in the study population. This was a 5 year study of 1,965 adult participants with paroxysmal A-Fib. Notably, the mean age was 69 years old. 45% of participants were women. The median CHA2DS2-VASc score of participants was 3. Participants wore a holter monitor for 14 days. All participants were untreated. The minimum and maximum durations of runs of paroxysmal A-Fib from this study were assigned for this scenario: 0.1 hours (6 minutes) and 30.4 hours (1824 minutes). Class I AHA/ACA recommendations for electrical cardioversion of A-Fib include: 1) When A-Fib with rapid ventricular response does not respond to pharmacologic cardioversion with ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure, 2) Hemodynamic instability, 3) When the symptoms are unacceptable to the patient (Fuster et al, 2006). In a best-case scenario episode of A-Fib, these sequelae are not anticipated. Thus, the need for emergent cardioversion (the chosen RTDC surrogate) would not exist. Therefore, the RTDC probability for best-case scenarios was assigned 0%. Per Barr, 2010 most astronauts have a CHADS2 score of 0-1. When the score is expanded to CHADS2-VASC, sex is also included. Accounting for sex, astronauts could have scores from 0-2. (Points being collected for being female and having hypertension). Lip et al, 2010, a prospective cohort study of A-Fib (from the EURO Heart Study) included patients without mitral stenosis, previous valvular surgeries, and not on anticoagulation. There were 0, 162 (0.6%), and 184 (1.6%) thromboembolic events in participants with CHADS2-Vasc scores of 0, 1, and 2 respectively. Thus, using thromboembolic events as a surrogate for mortality, the LOCL probability was assigned a range of 0-1.6%.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

The same values were used for duration and RTDC probability for this scenario as the treated worst-case scenario. The LOCL probability differs. The durations used were informed by Go et al, 2018 and relate to the total duration of multiple A-Fib episodes seen in the study population. This was a 5 year study of 1,965 adult participants with paroxysmal A-Fib. Notably, the mean age was 69 years old. 45% of participants were women. The median CHA2DS2-VASc score of participants was 3. Participants wore a holter monitor for 14 days. All participants were untreated. The minimum and maximum durations were assigned as 0.2 hours and 120 hours, respectively. Class I AHA/ACA recommendations for electrical cardioversion of A-Fib include: 1) When A-Fib with rapid ventricular response does not respond to pharmacologic cardioversion with ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure, 2) Hemodynamic instability, 3) When the symptoms are unacceptable to the patient (Fuster et al, 2006). The minimum RTDC probability of 10% was informed by Kanji et al, 2012. In this retrospective observational study, consecutive patients admitted to either medical or surgical adult ICUs in 3 Canadian hospitals between Jan 1 and Dec 31, 2006 were considered. 325 patients were identified as having A-Fib during their ICU stay, and of these, 139 cases were determined to be new-onset A-Fib. Hemodynamic instability developed in 10% of patients with new-onset A-Fib. The mean age of participants with new-onset A-Fib was 71.6 years and 60% of participants were male. Notably, the admitting diagnosis was A-Fib in only 6 patients. Otherwise, admitting diagnoses included (sepsis, respiratory failure/pneumonia, cardiogenic shock/cardiac arrest, CVA, post-operative care, and "other"). There were notably many comorbidities (e.g. smoking, asthma, COPD on oxygen, valvular heart disease, HTN, CHF, cardiomyopathy, CKD, history of CVA, and diabetes). 39% of patients with new-onset A-Fib were on either a beta blocker, calcium channel blocker, or digoxin prior to admission. The maximum RTDC probability of 59% was informed by Tischler et al, 1990 a retrospective review conducted at Brigham and Women's Hospital from Jan 1, 1985-Dec 31, 1988. 87 patients met the inclusion criteria of presumed new-onset A-Fib (symptoms less than 48 hours), and technically adequate echocardiograms performed while in sinus rhythm during the hospitalization. Mitral stenosis was excluded. Participants were classified as "unstable" if they met any of the following criteria: hypotension (SBP < 90mmHg), angina or chest pain with ST-segment depressions of at least 1 mm in at least 2 leads, congestive heart failure based on physical exam and x-ray, or witness syncopal episode. 59% of patients were considered unstable in this cohort. Notably, the average age of participants was 61 years for stable A-Fib patients, 66 years for unstable A-Fib patients. The study included nearly 50% female participants. Significant co-morbidities existed in the cohort. Despite the presumption of new-onset A-Fib, pre-existing A-Fib was documented in 31% of unstable patients. Other comorbidities included valvular issues (aortic stenosis /regurgitation, mitral regurgitation), hypertension, angina/MI, COPD. The probability of LOCL was assigned 0-10.18% based on all-cause mortality data presented in Lee et al, 2018 a retrospective cohort study of 15,411 patients with A-Fib, identified by ICD-10 code from a national database in South Korea between 2002-2013. Notably, only a third of the patients in this cohort were less than 60 years old. However, all-cause mortality was provided by decade of life, so the maximum probability value was derived by age restricting the data to decades 20s-50s (464 deaths in 4556 patients). The younger patients in this study had lower CHADS2-Vasc scores, indicating that fewer of these subjects were treated with anticoagulation. Similarly, fewer of these subjects were treated with anti-arrhythmics. Thus, by age restricting we may be selecting a largely "untreated" population. While valvular AF was excluded from this study, pre-existing co-morbidities of ischemic heart disease, prior myocardial infarction, and congestive heart failure existed in the patient population, which indicates that this may be an overestimate of LOCL probability.

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

Citation	Source	LOC Value
Go et al, 2018	Terrestrial	3

Duration values for all scenarios are driven by data from Paroxysmal A-Fib. The worst-case scenarios include recurrent episodes of paroxysmal A-Fib.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Fuster et al, 2006	Terrestrial	2
Tischler et al, 1990	Terrestrial	

Citation	Source	LOC Value
Kanji et al, 2012	Terrestrial	

The RTDC surrogate of need for emergent cardioversion was used. Tischler et al, 1990 and Kanji et al, 2012 present the proportion of A-Fib cases that are unstable (i.e. they warrant emergent cardioversion). Note, these may overestimate RTDC probability due to the age of the participants (60s-70s) and multiple comorbidities, including cardiac co-morbidities. Kanji et al, 2012 is specifically in an ICU population, which would be anticipated to be more ill than a non-ICU population. Regardless of these limitations, this was the best data available to inform these probabilities.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Lip et al, 2010	Terrestrial	2
Lee et al, 2018	Terrestrial	
Barr, 2010	Terrestrial	

LOCL probability values are driven by risk of thromboembolism (being used as a surrogate for mortality) for best-case scenarios (Lip et al, 2010). Thromboembolism incidence rates were selected for CHADS2-Vasc scores of 0-2 (the most likely scores for the astronaut cohort based on Barr, 2010). Using thromboembolism as a surrogate for mortality may overestimate LOCL probability. For the worst-case scenarios, all-cause mortality in patients with A-Fib from a National Database in South Korea was used (Lee et al, 2018). The data was age restricted for decades of life 30s-50s to better approximate the astronaut cohort. The population had multiple co-morbidities (including cardiac), thus the worst-case scenario estimates for LOCL may also be overestimates.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

ICL - 10, ATRIAL FIBRILLATION/ ATRIAL FLUTTER

Definitions:
Best Case: Atrial fibrillation or flutter that does not require emergent cardioversion, rate/rhythm control, or thromboembolic prophylaxis.
Worst Case: Atrial fibrillation or flutter that requires emergent cardioversion, rate/rhythm control, or thromboembolic prophylaxis.

Capabilities and Resourcing Scope

Overview
Atrial fibrillation occurs when diffuse or irregular electrical activity in the heart's atrium suppresses the typical sinus conduction pattern.1 Untreated, sustained atrial fibrillation leads to an increased risk of morbidity and mortality resulting in heart failure, venous thromboembolism (such as stroke or pulmonary embolism) or cardiogenic shock.2, 3 Patient presentation varies as some are asymptomatic and only discover the arrhythmia during routine screening; others may experience palpations, shortness of breath, exercise intolerance, chest pain or malaise. Atrial fibrillation can occur in persons with no predisposing conditions when associated with episodes of profound catecholamine surges or increased vagal tone. Severe emotional stressors or vigorous exercise have caused bouts of atrial fibrillation in otherwise healthy patients. Atrial fibrillation is often categorized as either paroxysmal, persistent, or permanent.3-5 In paroxysmal cases, episodes of atrial fibrillation terminate within seven days (and often within 24 hours) without any intervention. Persistent atrial fibrillation lasts more than seven days and requires either medication or a procedure to restore a regular conduction pattern. Permanent atrial fibrillation is not amenable to any medication or interventions to restore sinus rhythm.

In this CRT, the best-case definition refers to an episode of paroxysmal atrial fibrillation. The spaceflight crewmember may discover this episode incidentally during regular crew monitoring or have associated mild symptoms. The crewmember would revert to sinus rhythm within 24-48 hours without intervention.

The worst-case scenario would involve persistent or permanent atrial fibrillation. Albeit it would be expected that if untreated the worst case would lead to such complications such as venous thromboembolism, acute cardiac syndrome, or cardiogenic shock, this CRT does not include resources for these downstream conditions as they are provided for in other CRTs.

Diagnostic Scope and Resourcing
In the best case, diagnosis will likely be made via history, physical and electrocardiogram. However, at the time of identification, it will unknown whether this is the best-case or worst-case scenario as this will be differentiated by the chronicity of the arrhythmia. Consequently, resources allocated for CP1 are similar in both scenarios. Laboratory testing and cardiac ultrasounds are included to conduct simple differentials for common reversible causes of the arrythmia (anemia, electrolyte derangements, myocardial infarction, pulmonary embolism, pericardial effusion, hypovolemia). Thyroid testing is not included as crews would be screened for abnormalities preflight. A chest plain film (X-ray), which is commonly obtained in terrestrial scenarios, is unavailable inflight. Adenosine, which is sometimes used to differentiate between atrial fibrillation, atrial flutter and supraventricular tachycardia in cases of rapid heart rates, was decided to be beyond the scope of this condition by CRT subject matter expert consensus.

Clinical Phase 1 Duration and Rationale
This version of IMPACT presumes physician level knowledge, skill, and ability will be present on the mission. The CRT working group SME consensus duration is as follows:
CP1 BC (Treated or Untreated): 2.26 hours
This is the longest reasonable time to complete the task for an experienced clinician adjusted for being in the spaceflight environment 1) to remove a crewmember from duties 2) obtain a history 3) examine the patient 4) obtain an EKG 5) insert an intravenous line 6) perform blood work and 7)

obtain a cardiac ultrasound.
CP1 WC (Treated or Untreated): 2.43 hours
This is the same time allocated in the best-case condition with the addition of ground communications.

The highest scope of practice code used in this CRT which includes interpretation of diagnosis, performing diagnostic tests and performing treatment (particularly moderate sedation and synchronized cardioversion) would be a five: this is at the experienced procedural trained generalist attending (emergency medicine attending)

Treatment Scope and Resourcing
In the best-case scenario, treatment is limited to reversing all causes that may have elicited the arrhythmia. Optimizing crew-member hydration would be an expected course in addition to monitoring for arrythmia reoccurrence. Of note, platelet inhibitors, such as aspirin, are not indicated in atrial fibrillation. By its definition, the worst-case scenario requires intervention. The type of involvement will vary by the clinical scenario and cause of the arrhythmia. Consequently, resources for both rate and rhythm control are allocated. Of note, many common terrestrial medications that would be used in an emergency department, such as intravenous diltiazem or metoprolol are not on currently on spaceflight formulary but amiodarone which is a second-line medication for rate control of atrial fibrillation in patients with few comorbidities is available. In this CRT, it is expected that should immediate rhythm control be necessary, electrical cardioversion would be used as procainamide is not on formulary and has varying success rates of conversion. At least intermittent heart rhythm monitoring would be advised until end of mission. Medications that have weight-based dosing in this CRT have all been allocated for a 75 kg individual.

Communications and Support Needs
In the best-case scenario, diagnosis and course of treatment is uncomplicated and likely within the scope of care of onboard crew members. In the worst-case condition, ground communications are necessary as there might be uncertainty regarding rhythm and ultrasound interpretation and the course of treatment, particularly since treatment can include high-risk interventions.

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IMM CLIFF RECONCILATION COMMENTS

The best and worst-case scenario definitions have changed. The best-case scenario definition in the IMM Cliff was, “An isolated episode of lone atrial fibrillation or atrial flutter. There is low risk of thrombo-embolic events. The episode is asymptomatic or mildly symptomatic and/or resolves spontaneously. An underlying precipitating factor such as physical stress, infection, etc. may or may not be identified.” The current best-case scenario definition is, “Atrial fibrillation or flutter that does not require emergent cardioversion, rate/rhythm control, or thromboembolic prophylaxis.” The prior IMM definition of the worst-case scenario was, “New onset of atrial fibrillation or atrial flutter that is either symptomatic, sustained, or associated with complications requiring oral or intravenous treatment for rate or rhythm control, as well as prophylaxis for thrombo-embolic complications.” The current worst-case scenario definition is, “Atrial fibrillation or flutter that requires emergent cardioversion, rate/rhythm control, or thromboembolic prophylaxis.” These changes reflect an attempt to focus the current definitions on need for intervention/treatment. In the IMM CLiFF, the maximum duration for all scenarios was 72 hours. The maximum duration for the best-case scenarios in this CLiFF is 30.4 hours and worst-case scenarios is 127 hours. EVAC probability in the IMM CLiFF was 0-100% for best-case scenarios and 100% for worst-case scenarios. In the current CLiFF the RTDC probability is 0% for best-case scenarios and 10-59% for worst-case scenarios. IMM LOCL probability was 0% for all scenarios. In this CliFF it is 0-1.6% for best-case scenarios and 0-10.18% for worst-case scenarios.

LIMITATIONS SUMMARY

• The evidence informing the entire CLiFF is based primarily on A-Fib, rather than A-Flutter. • All durations were based on a single study of Paroxysmal A-Fib. By definition (see overview) paroxysmal A-Fib is brief episode lasting less than a week. Other types of A-Fib (persistent, long-term persistent, and permanent) obviously last longer with permanent being presumed to be life-long. • The RTDC surrogate of need for emergent cardioversion was used. Tischler et al, 1990 and Kanji et al, 2012 present the proportion of A-Fib cases that are unstable (i.e. they warrant emergent cardioversion). Note, these may overestimate RTDC probability due to the age of the participants (60s-70s) and multiple comorbidities, including cardiac co-morbidities. Kanji et al, 2012 is specifically in an ICU population, which would be anticipated to be more ill than a non-ICU population. Regardless of these limitations, this was the best data available to inform these probabilities. • LOCL probability values are driven by risk of thromboembolism (being used as a surrogate for mortality) for best-case scenarios (Lip et al, 2010). Thromboembolism incidence rates were selected for CHADS2-Vasc scores of 0-2 (the most likely scores for the astronaut cohort based on Barr, 2010). Using thromboembolism as a surrogate for mortality may overestimate LOCL probability. • LOCL probability values for the worst-case scenarios are based on all-cause mortality in patients with A-Fib from a National Database in South Korea (Lee et al, 2018). The data was age restricted for decades of life 30s-50s to better approximate the astronaut cohort. The population had multiple co-morbidities (including cardiac), thus the worst-case scenario estimates for LOCL may also be overestimates.

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)												
Untreated Best Case (UTBC)												
Treated Worst Case (TWC)		664					145					
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)	132							211	343	3763	0.0911507	9.11507
Treated Worst Case (TWC)	132		414	22	196	34	34	211	1852	3763	0.492161	49.2161
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)	132							211	343	3763	0.0911507	9.11507
Treated Worst Case (TWC)								211	211	3763	0.0560723	5.60723
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