Spaceflight Associated Neuro-ocular Syndrome CLIFF Peer Review

1. *Strength of evidence presented in CLIFF in modeling the characteristics and mission impact of this medical condition within the spaceflight environment?*

   Score: 2

   Grading Scale:

   4 - Confident

   3 - Somewhat confident

   2 – Neutral

   1 – Somewhat unconfident

   0 – Not confident

2. How confident are you that these data accurately represent the spaceflight environment?	*Tables 1, 2* *Composite Incidence and Level of Confidence*	*Table 3, 4 BC/WC* *Loss of Crew and probability*	*Table 4 - Clinical Phase 1, 2 durations* *Table 5 – CP 2 Loss of Crew*	*Table 4 – RTDC %* *Table 6 – RTDC Loss of Crew*	*Table 4 – Loss of Crew Life %* *Table 7 – Loss of Crew Life, Loss of Crew*	*Table 8 – TI*
Score	*2*	*3*	*3*	*3*	*3*	*3*

Comments and limitations:

1. **General comments.** This CLiFF characterizes Spaceflight Associated Neuro-Ocular (SANS) that has been documented during spaceflight in microgravity. Despite being widely studied since first described, the etiology and natural history of this condition are poorly understood. SANS constitutes a constellation of findings including thickening of the retina, changes in visual acuity, choroidal folds, papilledema, and presence of choroidal folds. The in-flight diagnosis is aided by measurement of visual acuity, ultrasound, and optical coherence tomography (OCT). Treatment includes use of corrective lenses, but preventive countermeasures are still being investigated. While idiopathic intracranial hypertension has some similarities, there is no exact terrestrial equivalent to SANS. The etiologies of SANS are widely debated, but long-term exposure to microgravity seems to be a necessary condition. Thus, it is difficult to know how operations in partial gravity will affect the onset and development of SANS. The best case is considered to be a greater than 55um but less than 200um change in total retinal thickness (TRT), presence of any choroidal folds, or visual acuity change >0.75 diopters in either eye measured during or post flight. The worst case is a greater than

200um change in total retinal thickness (TRT), choroidal folds overlying the fovea, or visual field defects with blind spots.

2. **Incidence.** There have been 7 documented cases of SANS out of 27 unique astronaut missions in which a full range of preflight, inflight, and postflight measurements were accomplished. One repeat flyer with SANS was eliminated from the calculations. This data from LSAH was used to calculate the estimated incidence. Analog experiments using head-down tilt measurements have been done, but these are widely felt to not accurately represent the conditions that lead to SANS. There is no terrestrial data to support the incidence estimation. An assumption is made that the incidence associated with missions in microgravity will be applicable to missions in partial gravity (lunar or Martian). There is no current data that can verify the validity of this assumption. Once surface operations begin, data will be collected to refine the incidence value. Based on a review of the data, the minimum flight time for onset of any feature of the SANS definition was estimated at 14 days as shuttle astronauts did experience visual changes. However, the minimum time noted for astronauts who underwent a full suite of testing and developed SANS was 60 days. The BC/WC split of 86/14% is based on the finding that 1 of the 7 reported cases met the worst case definition. The clinical phase durations are based on subject matter expertise. Treatment is currently the use of corrective lenses and periodic monitoring for progression of disease. RTDC and Loss of crew life probabilities are zero based on the case definitions and CST consensus, and I am in agreement with their calculation. The probability density curve that was derived appears to be a reasonable representation of the data presented.

3. **Clinical phase data**. I am in agreement with the clinical phase 1 duration entered in this CLIFF. This data was compiled by a team of expert clinicians, and I was involved in the discussions leading to the calculation of the clinical phase duration. CP2 was supported by terrestrial evidence.

4. **Task impairment**. The analysis was performed and reviewed by a separate team of expert clinicians. I am aware of the methods that were used but did not directly participate in the discussions.

5. **Dependence on mission phase or duration of mission**. This medical condition may be dependent on mission phase since all cases have been associated with spaceflight in microgravity. It is not yet known what the incidence will be in a partial G environment. Also, there is a minimum time needed in microgravity to develop SANS.

6. **Limitations**

- This medical condition may be dependent on mission phase since all cases have been associated with spaceflight in microgravity. It is not yet known what the incidence will be in a partial G environment. Also, there is a minimum time to develop SANS.
- The etiologies of SANS are widely debated, but long-term exposure to microgravity seems to be a necessary condition. Thus, it is difficult to know how operations in partial gravity will affect the onset and development of SANS.
- An assumption is made that the incidence associated with missions in microgravity will be applicable to missions in partial gravity (lunar or Martian). There is no current data that can verify the validity of this assumption. Once surface operations begin, data will be collected to refine the incidence value.
- The definition of SANS has changed over time as we understand more about this disease. The definitions used here were created during the development of this CLIFF

and are up to date but are also likely to be inaccurate over time as more research provides insight into the pathophysiology of SANS.

- Some of the ocular abnormalities found in flight have unclear clinical significance. Some astronauts with substantial retinal thickening do not have any visual changes and others with minimal changes in retinal thickness do report visual changes.
- The natural history of SANS is unknown. There is concern that over time vision will continue to worsen; however, this has not been verified by the data as yet. Long duration missions may have a higher incidence and impact from SANS than the shorter duration missions that were the source for our data.
- Access to the SANS dataset is limited to a small number of individuals as it is a spaceflight specific condition and protected under LSAH for astronaut health privacy.
- 28 of the 34 person missions studied had complete testing. Cases in which there was incomplete testing were removed as was any return fliers as we do not know if having SANS increases a crew member's likelihood of having it on subsequent missions. The total unique astronauts used was 27.
- Mission duration also appears to have an impact on incidence of SANS; however, there are reports of visual changes among shuttle astronauts which implies a relatively rapid onset of these findings. Within the data set used to calculate the incidence, 60 days is the shortest duration, and 1 year is the longest.
- The worst-case definition was agreed upon with the SANS research group. It includes the criteria "choroidal folds involving the retina" and "visual field defects" which are theoretical severe outcomes but have never been observed. The 3rd criterion "TRT>200 microns" was found in an astronaut with limited visual changes and no increase in ICP. As discussed, the severity or long-term changes associated with SANS are unknown and thus criteria from our WC scenario may not be possible or clinically relevant.
- CP2 duration was determined to range from 0-12 hours; however, this may not accurately represent the treatment time. There is no treatment for SANS other than visual correction with glasses. It is also not clear if elevated ICP is clearly associated with this condition; thus, there are no interventions required to prevent hydrocephalus. 12 hours was taken as the maximum CP2 duration to account for time spent observing the patient, finding necessary equipment, and time to return to work.

Reviewed by:

David C. Hilmers