Surveillance of Ocular Parameters and Visual Function in Bed Rest Subjects

BACKGROUND AND SIGNIFICANCE

Ocular Changes Related to Spaceflight

Recent visual changes in astronauts have raised concern about ocular health during long duration spaceflight. Seven cases have been documented in astronauts who spent 6 months aboard the International Space Station. These astronauts were male ranging in age from 45 to 55 years old. All astronauts exhibited pre- to post flight refractive changes. Decreased intraocular pressure (IOP) post flight was observed in 3 cases. Fundoscopic exams revealed post flight findings of choroidal folds in 4 cases, optic disc edema in 5 cases and the presence of cotton wool spots in 3 cases. Optical coherence tomography (OCT) confirmed findings of choroidal folds and disc edema, and also documented retinal nerve fiber layer thickening (5 cases). Findings from MRI examinations showed posterior globe flattening (5 cases), optic nerve sheath distention (6 cases) and torturous optic nerves (2 cases). Of the 7 cases, intracranial pressure was measured on 4 astronauts. These 4 showed elevated ICP post-flight that remained elevated for as long as 19 months in one case. These astronaut cases are summarized in Table 1.

While the etiology remains unknown, hypotheses speculate that venous insufficiency or hypertension in the brain caused by cephalad fluid shifts during spaceflight are possible mechanisms for ocular changes seen in astronauts. Head-down tilt bed rest is a spaceflight analog that induces cephalad fluid shifts. This study is designed to provide ocular monitoring of bed rest subjects and determine whether clinically relevant changes are found.

Ocular Changes Related to Bed Rest

Ocular changes related to changes in body posture are described in the literature for a variety of time lengths and body angles. Acute changes in intraocular pressure (IOP) are well documented for short duration studies ranging from 2 minutes to 48 hours (Longo et al., 2004; Xu et al., 2010; Kaeser et al., 2005; Carlson et al., 1987; Mader et al.,1990; Frey et al.,1993). In these studies, IOP showed an immediate increase when the body was placed in a recumbent position. This increase in IOP ranged from 2 – 5 mmHg and was the case for body angles of 0° (Kaeser et al., 2005), -8° (Longo et al., 2004), -10° (Mader et al., 1990; Frey et al., 1993), -15° (Xu et al., 2010; Carlson et al., 1987) and –50° (Carlson et al.; 1987). IOP demonstrated diurnal variations in a –10° position over the course of 48 hours showing a drop in IOP at night (Mader et al.,1990). Increased IOP was accompanied by a drop in heart rate (Longo et al., 2004; Kaeser et al.,2005), and changes in blood pressure (Xu et al., 2010; Longo et al., 2004; Kaeser et al., 2005). These studies documented decreased diastolic blood pressure. However, systolic blood pressure varied depending upon the time spent in the recumbent position. At the end of 2 minutes, no change was seen in systolic blood pressure (Longo et al., 2004). In contrast at the end of 21 and 30 minutes at –15° and 0° respectively, systolic blood pressure decreased (Xu et al., 2010; Kaeser et al., 2005). This change was gradual reaching a significant change at 6 minutes (Xu et al., 2010).

Calculated values of ocular perfusion pressure (OPP) increased in response to 2, 21 an 30 minutes of body tilt at –8°, -15° and 0° respectively (Longo et al., 2004; Xu et al., 2010; Kaeser et al., 2005). In one study, measurements of subfoveal choroidal blood flow (ChBF) demonstrated an 11% increase after 2 minutes at –8° tilt. This ChBF increase was due primarily to changes in choroidal blood velocity as choroidal blood volume did not change (Longo et al., 2004). In another study, ChBF demonstrated a 12% decrease in response to 30 minutes in a body position of 0° (Kaeser et al., 2005). These authors then recalculated OPP as they believed the ophthalmic arterial blood pressure used to calculate OPP was overestimated. Recalculation of OPP plotted against ChBF demonstrated that both variables decreased uniformly. The contrasting findings of these studies were explained by the differences in the time frame of each study (Kaeser et al., 2005). The authors of these studies however, came to the same conclusion that similarity in changes of OPP and ChBF suggest a passive response to changes in body posture.

Table 1. Summary of Ocular Changes in Astronauts

ISS Crew Member	*Mission Duration*	*Refractive Change*	*Intraocular Pressure mmHg*	*Fundoscopic Exam Post-Flight*	*Disc Edema (Frisen)*	*OCT Post-Flight*	*Eye MRI Post-Flight* *Globe Flattening*	*CSF Pressure Post-Flight cmH20*
CASE 1	6 months	Pre-flight: OD: -1.50 sph OS: -2.25-0.25x135 Post-flight: OD: -1.25 -0.25x005 OS: -2.50-0.25x160	Pre flight: 15 OU Post flight: 10 OU	• Choroidal folds (OD) • Cotton wool spot (OD)	Edema: No disc edema	Not performed	MRI not performed Globe Flattening: Not assessed	Not Measured
CASE 2	6 months	Pre-flight: OD: +0.75 OS: +0.50-0.25x165 Post-flight: OD: +2.00 sph OS: +2.00-0.50x140	Pre flight: 14 OU Post flight: 14 OU	• Bilateral disc edema (OD>OS) • Choroidal folds (OD>OS) • Cotton wool spot OS	Edema: Grade 1 OD and OS	• NFL thickening c / w disc edema	Mild optic nerve sheath distension (OD and OS) Globe Flattening: OD and OS	Elevated • 22 at R+66 days; • 26 at R+ 17 months; • 22 at R+19 months)
CASE 3	6 months	Pre-flight: OD: -0.50 sph OS: -0.25 sph Post-flight: Plano (0.00) Plano (0.00)	Pre flight: 10 OU Post flight: 10 OU	• Bilateral disc edema (OD>OS) • Small hemorrhage OD	Edema: Grade 3 OD Grade 1 OS	• Severe NFL thickening (OD>OS) c /w Disc edema	Mild optic nerve sheath distention (OD) Globe Flattening: None observed	Elevated • 21 at R+19 days;
CASE 4	6 months	Pre-flight: OD: -0.75-0.50x100 OS: plano (0.00)-0.50x090 Post-flight: OD: +0.75-0.50x105 OS: +0.75-0.75x090	Pre flight: 15/13 Post flight: 11/10	• Disc edema (OD) • Choroidal folds (OD)	Edema: Grade 1 OD	• Mild NFL thickening (OD>OS) c/w disc edema • Choroidal folds (OD)	Distended optic nerve sheaths and tortuous optic nerves (OD>OS) Globe Flattening: OD > OS	Elevated • 28.5 at R+57 days;
CASE 5	6 months	Pre-flight: OD: -5.75-1.25x010 OS: -5.00-1.50x180 Post-flight: OD: -5.00-1.50x015 OS: -4.75-1.75x170	Pre flight: 14/12 Post flight: 14/12	• Normal	Edema: No disc edema	• Subclinical disc edema • Mild/moderate NFL thickening (OD only)	Distended optic nerve sheaths and tortuous optic nerves Globe Flattening: OD and OS	Not Measured
CASE 6	6 months	Pre-flight: OD: +0.25 OS: +0.25-0.50x152 Post-flight: OD: +2.00-0.50x028 OS: +1.00 sph	Pre flight: 14 OU Post flight: 14 OU	• Disc edema (OD) • Cotton wool spot (OS)	Edema: Grade 1 OD	• Mild NFL thickening c/w disc edema • Choroidal folds (OD)	Distended optic nerve sheaths (OD>OS) Globe Flattening: OD > OS	Not Measured
CASE 7	6 months	Pre-flight: OD: +1.25 sph OS: +1.25 sph Post-flight: OD: +2.75 sph OS: +2.50 sph	Pre flight: 16 OU Post flight: 12/14	• Disc edema (OU) • Choroidal folds (OD>OS)	Edema: Grade 1 OD and OS	• Moderate NFL thickening c/w disc edema (OD and OS) • Choroidal folds (OD and OS)	Optic Nerve sheath distention OD and OS Globe Flattening: OD and OS	Elevated 28 at R+12 days

Notes. OD (oculus dexter) = right eye; OS (oculus sinister) = left eye; OU (oculi uterque) = both eyes; sph = sphere; NFL = nerve fiber layer (retina).

The caliber of retinal veins and arteries demonstrated an immediate decrease in response to a –10° position (Mader et al., 1990; Frey et al., 1993). This immediate response was not progressive as values remained the same after 48 hours of –10° bed rest. These changes in retinal veins and arteries may be an autoregulatory response that acts to maintain retinal perfusion (Mader et al., 1990). Changes in caliber of retinal veins and arteries correlated with decreased velocity of the middle cerebral artery. The authors hypothesized that increased cerebral venous and capillary pressures could elicit a dilation response in larger cerebral vessels like the middle cerebral artery (Frey et al., 1993).

Cephalad shifts of body fluids in response to tilt may be a factor responsible for increased IOP. Thoracic fluid index was measured in conjunction with IOP over 48 hours of bed rest at –10° (Frey et al., 1993). By 12 hours, thoracic fluid index increased demonstrating a decrease in thoracic fluids. This change remained after 48 hours of bed rest and paralleled the increase in IOP (Frey et al., 1993). Longer duration of bed rest has produced differing results due to the ability to follow these responses for a longer period of time (Chiquet et al., 2003). Chiquet and colleagues (2003) first examined acute changes in IOP as subjects moved from sitting to supine (0°). These changes were similar to those reported by others where values demonstrated an increase in IOP over this time frame (Xu et al., 2010; Longo et al., 2004). When studied over 7 days of –6° bed rest, IOP showed a progressive decrease when measured on days 1, 3, 5 and 7 (Chiquet et al., 2003). This decrease was significant by days 5 and 7. The drop in IOP resolved to baseline levels within 2 days following bed rest. Plasma volume measures paralleled IOP showing a progressive decrease that was significant by day 7 of bed rest. Correlation of IOP and plasma volume changes during bed rest was significant ($r = 0.61$, $p = 0.02$).

Cephalad fluid shifts may also play a role in intracranial pressure (ICP) dynamics (Steinbach et al., 2005). ICP dynamics were examined using ultrasound techniques before and after 30 days of –6° bed rest. Measures were taken with subjects in the 0° position. Ultrasound measured oscillations of the temporal bone to capture small displacements that occur during systole and diastole. Changes in compliance of these movements are related to ICP changes. Displacement amplitudes significantly decreased by 10 μm indicating altered intracranial compliance. Post bed rest amplitudes were similar to those of upright posture indicating a possible decrease in ICP by the end of bed rest.

Studies of longer duration bed rest have reported differing results. Mekjavic and colleagues (2002) measured visual acuity, IOP, stereo vision, contrast sensitivity and visual field over 35 days of 0° bed rest. Subjects were measured pre- and post bed rest. No differences from baseline for any of these measures were found. The lack of difference may partially be explained by the timing of post bed rest measures. Post bed rest measures were collected on the 2nd or 3rd day after bed rest. Based on the findings for IOP described above (Chiquet et al., 2003), changes in dependent measures may have already resolved by 2 days following bed rest.

A descriptive study examining 70 days of 0° bed rest reported decreased IOP, reduced visual field, increased blind spot, reduced visual acuity and a more distant near point of clear vision (Drozdova et al., 1969). By 20 days following bed rest, changes in blind spot and visual acuity were not fully resolved. The descriptive information presented in this study was not rigorously analyzed and should be interpreted with caution.

Preliminary Studies

Five head-down tilt bed rest subjects were recently monitored for the presence of ocular changes. Four subjects participated in 30 days of bed rest. One subject participated in 60-days of bed rest. At the time when ocular examinations were implemented, 3 subjects had already entered the bed rest phase. Therefore, pre-bed rest information was not available for these subjects. In addition to the ocular examination, the subject in the 60-day study also received 2 MRI scans of the head and eye. MRI scans were done approximately 2 weeks into the bed rest phase and during post bed rest. Below is a summary of the findings from these subjects.

> **60-day Subject:** Post study OCT and eye exam were within normal limits. No change in MRI from the in bed rest scan to post bed rest. Post study eye exam showed no documented evidence of disc edema or choroidal folds.

30-day Subject 1: Post study eye exam showed no documented evidence of disc edema or choroidal folds; however, post study OCT showed possible retinal nerve fiber layer thickening (no pre-test comparison available) which could be suggestive of mild retinal nerve fiber layer edema.

30-day Subject 2: Post study clinical exam showed no documented evidence of disc edema or choroidal folds; however, post study OCT showed possible retinal nerve fiber layer thickening (no pre-test comparison available). This could be suggestive of mild retinal nerve fiber layer edema.

30-day Subject 3: Normal eye exam pre- and post bed rest. No documented evidence of disc edema or choroidal folds. Possible mild retinal nerve fiber layer thickening on OCT post-bed rest with enlarged blind spot on visual fields.

30-day Subject 4: Subject complained of distance vision problems post bed rest. Eye exam showed a change in uncorrected distant visual acuity form 20/20 (right eye) and 20/25 (left eye) in pre-bed rest to 20/40 in both eyes at the post bed rest exam. Based upon pre- and post refraction results, the change in acuity appears to be due to change in astigmatism correction. OCT results were within normal limits. There was a negligible change in retinal nerve fiber layer thickness from pre- to post bed rest with no evidence of edema. Clinical exam was unremarkable with no evidence of optic disc edema or choroidal folds.

METHODS

Subjects

Subjects will be healthy adults selected from the general population of various age, gender, and ethnicity categories. The number of subjects participating in this study will be up to the discretion of the Data and Safety Monitoring Board (DSMB) for Ocular Safety in Bed Rest Studies.

Subjects will be selected using the NASA Flight Analogs Project standard screening procedures for bed rest studies. Subjects included in the study will 1) be 24-55 years old; 2) be between 60 – 75 inches tall; 3) have a body mass index between 18.5 and 30; 4) have bone mineral density within 2 standard deviations of normal when measured at the hip using a DXA scan. Subjects will be required to pass 1) a modified Air Force Class III Physical examination; 2) screening for HIV and hepatitis A, B and C; 3) screening for illegal drug and alcohol use; and 4) psychological screening. Screening for ocular health is incorporated into the modified Air Force Class III Physical. In addition, subjects will be tested for color blindness.

Subjects will be excluded from the study who:

1) require medication that may interfere with interpretation of the results
2) have a recent sub-standard nutritional status
3) have a history of thyroid dysfunction, renal stones, mental illness, or smoking within six months prior to the start of the study
4) have a family history of thrombosis
5) are using hormonal contraceptives
6) are peri- or post menopausal
7) cannot clear a criminal background check
8) are currently on bis-phosphonate therapy
9) have a positive pregnancy test (females)
10) have a history of gastroesophageal reflux disease
11) have medical implants that would interfere with MRI testing
12) are color blind

Conditions of Bed Rest

This study will be conducted at the NASA Flight Analogs Research Unit at the University of Texas Medical Branch in Galveston, TX. Because this surveillance study will be used in conjunction with other studies being conducted at the Flight Analogs Research Unit, times spent in the pre-, in and post bed rest phases may vary. In general, subjects will spend 13 days in pre-bed rest where they remain ambulatory and undergo pre-testing. During the bed rest phase, subjects will spend 60 days in the 6° head-down tilt position. Testing will be conducted during this phase. During post bed rest, subjects will again be ambulatory and spend 14 days participating in post bed rest testing. Due to their de-conditioned state, subjects will also receive rehabilitation during this period.

This study will adhere to conditions as standardized for all NASA bed rest studies. These conditions are listed below.

1) Room Temperature: 72 degrees F. (+/- 2 degrees);
2) Humidity: 70% (+/- 5 percent);
3) Awaken at 06:00, lights out at 22:00, 7 days per week, no napping is permitted;
4) Monitoring by a subject monitor and an in room camera;
5) Daily 24-hour urine collection;
6) Daily measures: blood pressure, heart rate, temperature, respiratory rate, body weight fluid intake and output;
7) A standardized diet is consumed;
8) Daily iron supplementation (2ml ferrous sulfate elixir (17.6 mg elemental iron)) for all women, and men who are less than 35 ng/ml ferritin at screening;
9) Daily Vitamin D supplementation at 800 IU;
10) Minimum fluid intake of 28.5 ml/kg of body weight (2000 ml fluid for 70 kg) each day;
11) Activity: subjects may visit with each other, hospital and study staff, read, speak on the telephone, listen to the radio, watch television, or use computers during waking hours;
12) Visitation: outside visitors must receive advanced approval;
13) A twice daily stretching exercise regimen is required;
14) Regular therapeutic massage is planned;
15) Psychological support is provided once weekly during the study and available as needed at all times.

Ocular Examinations

Ocular examinations as recommended by the DSMB will be used as required for bed rest studies. The ocular examination consists of tests used when visiting an ophthalmologist's office. These standard medical tests are non-invasive and should not cause significant discomfort to the subjects. Examinations will be completed routinely throughout all phases of the bed rest study. Most tests will be completed on a weekly schedule. For a summary of the testing schedule, see Table 2. Examinations will include the following measures:

Review of Systems Questionnaire – This questionnaire is used to ask subjects if they experienced any physical symptoms in the past week. Questions regarding eye health are included. This questionnaire will be administered weekly in all phases of the bed rest study. A copy of the questionnaire is attached in the Appendix.

Best Corrected Visual Acuity (near and far) - Visual acuity is a measure of the spatial resolution of the visual processing system. Corrective lenses are used if needed by the subject to achieve their best performance (Vaughn et al., 1999). This test will be administered weekly during all phases of the bed rest study.

Cycloplegic Refraction - Refraction is the procedure by which the natural optical error is characterized and quantified. This procedure helps to distinguish between blurred vision caused by refractive error

and medical abnormalities of the visual system. Cycloplegic refraction refers to refraction done with a cycloplegic agent to dilate the pupil. The cycloplegic agent is used to overcome accommodation by paralyzing the ciliary muscle so that the absolute refractive error can be measured (Vaughn et al., 1999). This test will be done weekly during all phases of the bed rest study.

Modified Amsler grid testing - The Amsler grid is a grid of horizontal and vertical lines used to evaluate the central visual field for damage to the macula or optic nerve. In this test, the person looks with each eye separately at a small dot in the center of the grid composed by black lines on a white background. Wavy, blurred, distorted lines or missing areas of the grid may be indicative of retinal disturbances (Vaughn et al., 1999; Segre, 2009). This test will be completed weekly during all phases of the bed rest study.

Red Dot test – The Red Dot test is used to evaluate visual fields. The person focuses their vision on a black dot centered within a circle of red dots located 14" (33cm) away. The person looks at the center black dot and indicates whether or not all the red dots can be seen. Each eye is examined separately by covering the opposite eye. Corrective lenses are worn if needed. Inability to see the black dot or any of the red dots suggests a visual field deficit. This is an excellent and rapid screening tool when used with the Amsler grid test. This test will be completed weekly during all phases of the bed rest study.

Confrontational Visual Field testing - This test is used to assess peripheral vision. The subject covers one eye while the other fixates a point straight ahead. A target is moved from the far periphery to the near periphery in each of the visual quadrants. Subjects are asked to indicate when the target appears in their field of view. This test will be completed weekly during all phases of the bed rest study.

Color Vision testing – For color vision testing, subjects identify shapes that vary in color and intensity and lie within a background of dots. The type and degree of color vision deficiency is then assessed based upon subject's responses. Hardy-Rand-Rittler plates will be used for this purpose as results are less dependent on the degree of visual acuity (McCulley et al., 2006). This test will be done weekly in all phases of the bed rest study.

Tonometry – Applanation tonometry will be used to assess IOP. Using this method, IOP is determined by the amount of force required to flatten the cornea by a specified standard amount. Because the instrument is placed on the eye, a topical anesthetic is used to numb the eye prior to taking the measure (Vaughn et al., 1999). Measures will be taken weekly in all phases of the bed rest study.

Non-mydriatic Fundus Photography - This test allows the examination of the posterior segment of the eye, mainly the retina and optic disc. The subject is directed to look straight ahead at a distant object. The ophthalmoscope illuminates the retina through the pupil. Structures that are observed lie in the innermost aspect of the globe: retina, retinal blood vessels, optic nerve head (disc), and to a limited degree, subjacent choroid (Vaughn et al., 1999). This test will be done in pre- and post bed rest. During bed rest this test will be done at the study midpoint.

Optical coherence tomography - OCT is a noninvasive, noncontact, transpupillary imaging technology that can image retinal structures in vivo with a resolution of 10 - 17 microns. Cross-sectional images of the retina are produced using the optical backscattering of light. The anatomic layers within the retina can be differentiated and retinal thickness can be measured (NYEEI**,** 2010). This test will be completed once during pre-bed rest, at the midpoint during bed rest, and twice during post bed rest.

Equipment for the non-mydriatic fundus photography and OCT tests require that the subject be seated during testing. These tests will be done at the mid-point during bed rest studies to avoid as much as possible

violation of the 6° head-down tilt position. For 14-day bed rest studies, these two tests (non-mydriatic fundus photography and OCT) will only be completed in the pre- and post bed rest phases. The tests will not be done during bed rest in a 14-day study.

Table 2. Sample Testing Schedule for a 60-day Study

	Pre-Bed Rest		In Bed Rest								Post Bed Rest	
Test	**BR-8**	**BR-1**	**BR7**	**BR14**	**BR21**	**BR28**	**BR35**	**BR42**	**BR49**	**BR56**	**BR+2**	**BR+9**
Review of Systems Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X
Best Corrected Visual Acuity	X	X	X	X	X	X	X	X	X	X	X	X
Cycloplegic Refraction	X	X	X	X	X	X	X	X	X	X	X	X
Amsler Grid Testing	X	X	X	X	X	X	X	X	X	X	X	X
Red Dot Testing	X	X	X	X	X	X	X	X	X	X	X	X
Confrontational Visual Fields	X	X	X	X	X	X	X	X	X	X	X	X
Color Vision Testing	X	X	X	X	X	X	X	X	X	X	X	X
Extraocular Muscle Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X
Non-mydriatic Fundus Photography	X					X					X	X
Optical Coherence Tomography	X					X					X	X

Statistical Analysis

Members of the NASA Biostatistics lab have been recruited for the planning and execution of our analytic strategy. Prior to analysis, we will perform an initial screening of the data to identify potential errors or outliers. STATA IC (v. 11.1) software will be used for our analyses. Because this proposal is designed as primarily a monitoring study focusing on clinical changes at the level of the individual, most of the analytics of this study will be made by clinicians on a per-patient basis. We have no comparison groups in the proposed study, however, so we are somewhat limited in terms of the statistical sophistication with which we can approach the data. Nevertheless, we are able to extract some group-level information from the proposed measures in this study that we can use for descriptive purposes. In particular, we will use a saturated two-level multilevel regression model to calculate confidence intervals for mean change from baseline at various time points during and after bed rest (see Table 2). Additionally, we will calculate measures of association such as Pearson correlation or Kendall's Tau (Kendall et al., 1990), between changes in ocular function (e.g. Best Corrected Visual Acuity) and changes in ocular structure (e.g. OCT), both overall and through time. We will also consider the possibility that changes in structure could precede changes in function in our analyses.

In addition, nonparametric regression or other methods of functional data analysis (Ramsay et al., 2006) will be used to develop trend models over bed rest and during recovery for each of the key outcomes. Examples of functional data analysis include spline regression, exponential decay models, lowess smoothing, and fractional polynomial modeling. We do not have specific hypotheses about how our vision and/or function

outcomes are likely to change, however, we do anticipate change to be non-linear, and not necessarily monotone in time, correlating with the physiological adaptation to the fluid and/or pressure shifts associated with head-down tilt. For example, we may see immediate and sharp changes observed following subjects' being placed head-down, with subsequent changes being more gradual or diminishing altogether. We generally anticipate these outcomes to return to normal or close-to-normal, but exactly when and how quickly we do not fully understand, thus functional data analysis will help us characterize the patterns in our data.

Statistical assumptions will be tested in concert with all techniques, and appropriate data transformations will be employed as needed in order to meet these assumptions. In the event that the proposed statistical plan cannot be conducted even after reasonable data transformations have been applied, we will revert to alternative non-parametric techniques as necessary.

Limitations

As stated above, the design of the proposed study permits primarily a descriptive analysis of observed changes (or not) over time on several outcomes of interest. We have no comparison group in this study; however our proposed longitudinal modeling techniques will permit us to compare pre-bed rest observations to later observations made during or after bed rest. Equivalency (or "no-difference") conclusions drawn from the proposed single-group pilot study are not to be inferred, nor warranted. As promising as it may be to find *non*-significant differences between pre- and post bed rest, this does *not* imply equivalence; there may have been systematic differences that were too small to detect at traditionally held alpha = 0.05 levels with the sample size we will obtain. Equivalency ("no-difference") conclusions would require a-priori criterion for equivalence, different statistical methods, relevant control group(s) if desired, and most likely a large sample size (Blackwelder, 1982).

DATA AND SAFETY MONITORING

Data and Safety Monitoring Board

This study will utilize a DSMB. The purpose for using the DSMB is to monitor ocular safety of bed rest subjects. Based on their review of the data, the DSMB will determine the safety of head-down tilt bed rest with regard to ocular health. The services of Theradex®, an international contract research organization (http://www.theradex.com/), were used to establish and will coordinate the DSMB. Theradex® has significant experience in this area and will ensure independence of membership and unbiased review of study results. DSMB members were selected by Theradex® and include clinicians with expertise in relevant clinical specialties. See Table 3 for the members included in the DSMB.

Table 3. Members of the DSMB

DSMB Member	Title & Affiliation	Specialty
Laurence B. McCullough, Ph.D. DSMB Chair	Associate Director for Education Medical Ethics Chair Baylor college of Medicine	Medical Ethics
W. Andrew Kofke, MD	Professor of Anesthesiology & Critical Care University of Pennsylvania	Neurocritical Care
Neil R. Miller, MD	Professor of Neuro-Ophthalmology Johns Hopkins University	Neuro-Ophthalmology
James Provenzale, MD	Professor of Radiology Duke University Emory University	Neuroradiology
Andrew Lee, MD	Chair of Ophthalmology Methodist Hospital Houston Professor of Ophthalmology, Neurology and Neurosurgery	Neuro-Ophthalmology

On December 10, 2010, a meeting of the DSMB was held. At that meeting, members voted to allow the restart of NASA head-down tilt bed rest studies. They agreed on the ocular tests necessary to assess safety. Those tests are included in this protocol. Further, they provided a plan that identified thresholds for abnormal findings and follow-up diagnostic testing for serious findings. That plan is outlined below.

The DSMB is to be notified of the following abnormal findings:

- Visual acuity change greater than .5 diopters that persists beyond 24-48 hours and cannot be corrected to baseline with the use of corrective lenses
- Acquired color vision defects
- Changes in visual non-mydriatic fundus photography
- Increase in IOP that exceeds a value of 25 mmHg
- Visual field defects persisting beyond 48 hours

The DSMB requested diagnostic follow-up tests for the conditions listed below.

Magnetic Resonance Imaging (MRI) is indicated for:

- Presence of choroidal folds alone. A complete ophthalmology exam would also be done.
- Unremitting headaches. A neurology consult would also be called.

MRI, Lumbar Puncture (LP) and Neurology Consult are indicated for:

- Papilledema
- Cranial nerve paresis
- Pulsatile tinnitus
- Unremitting nausea and vomiting

Results of any follow up testing including MRI, LP and neurology consults will be reported to the DSMB. Once notified, the DSMB will determine conditions under which the subject and/or the study may or may not continue.

The DSMB may also be involved in review of any individual event thought to be of major significance by the attending physician or the NASA Flight Analogs Project Scientist. These events would generally be serious outcomes for which a causal connection with the study is plausible. The attending physician and the NASA Flight Analogs Project Scientist will also utilize the expertise of the DSMB to assist in determination of adverse events if needed.

In addition to event reporting, a routine quarterly report will be submitted to the DSMB by the NASA Flight Analogs Project Scientist. These reports and any responses generated by the DSMB will be distributed to the study sponsor, the investigator team, NASA CPHS, UTMB IRB and the UTMB Institute for Translational Sciences-Clinical Research Center (ITS-CRC). These reports will help to determine relative risk to the subjects, and make recommendations for protocol modifications and study continuation.

Health and Safety Monitoring

The attending physician at the Flight Analogs Research Unit is responsible for ensuring that appropriate medical care and medical coverage is provided to all subjects participating in this study. The attending physician is responsible for the overall health of the subjects, makes daily rounds, and responds to any medical complaints. This responsibility may be delegated to a qualified UTMB physician collaborator who possesses the requisite clinical expertise and patient care privileges.

As required by the NASA CPHS, safety monitoring of individual testing sessions is carried out by physicians in accordance with the levels specified below. A medical monitoring level is suggested by the investigator and evaluated by the CPHS. These levels are described below. For the medical testing in this study, all tests will be conducted under the direction of a qualified physician.

Level 1

- Typically for invasive or highly provocative procedures or for protocols that require maximal aerobic exertion
- Physician with current Advanced Cardiac Life Support training is present at the time of the test and is actively monitoring the test subject.
- A crash cart is available in the immediate vicinity of the test
- Two personnel with current Basic Life Support-Automated External Defibrillator training are present during testing
- Quarterly emergency drills are conducted by the investigator team
- Protocol Compliance Officer is made aware of the test and emergency drill schedules

Level 2

- Typically for modestly provocative procedures carrying more than minimal risk such as those that require sub-maximal aerobic exertion of >85% of maximum predicted heart rate or oxygen consumption (VO2)
- Physician with current Advanced Cardiac Life Support training is able to reach the testing area within two minutes
- A crash cart is available in the immediate vicinity of the test.
- Two personnel with current Basic Life Support-Automated External Defibrillator training are present during testing
- Quarterly emergency drills are conducted by the investigator team
- Protocol Compliance Officer is made aware of the test and emergency drill schedules

Level 3

- Typically for procedures that carry less risk than Level 2 procedures, for example those that require sub-maximal aerobic exertion of <85% of maximum predicted heart rate or VO2
- Physician with current Advanced Cardiac Life Support training is available within 15 minutes of notification
- Two Basic Life Support-Automated External Defibrillator certified personnel can respond to the test site within two minutes
- An Automated External Defibrillator is located nearby and available for use within two minutes

Level 4

- Typically for minimal risk procedures
- Physician is aware of the specific testing and is available for telephone consultation

UTMB Rapid Response Team

For testing done at the Flight Analogs Research Unit, if some medical emergency occurs during the procedure, the UTMB ITS-CRC Nurse will call the Rapid Response Team or call a Code, depending on the nature and severity of the medical emergency. The rapid response team (RRT) is committed to providing critical care resources to patients who may be in crisis. The RRT is composed of an ICU trained Registered Nurse, a Respiratory Therapist, and a Nurse Administrator. A physician order is not required for Rapid Response activation, but all treatments and interventions require a physician's order. For testing at UTMB not conducted on the Flight Analogs Research Unit, any healthcare provider may activate the Rapid Response Team by dialing the operator at extension 24000. The caller is to provide their name and extension and the location by unit and building.

When an adverse indicator is noted, the patient's physician shall be notified of changes indicating deterioration in the patient's condition. The nurse or other health care provider assigned to the patient may activate the Rapid Response Team to assist with assessment and timely treatment when a patient's condition is questionable or when a change in the patient's status falls within the following parameters:

1. Staff member concerned/worried about the patient.
2. Acute change in heart rate (less than 40 or greater than 130)
3. Acute change in systolic blood pressure (less than 90mm/Hg)
4. Acute change in respiratory rate (less than 8 or greater than 28) or threatened airway
5. Acute change in oxygen saturation (less than 90%)
6. Acute change in level of consciousness
7. Acute significant bleeding
8. Patient's oxygen requirements increase (50% or greater)
9. New, repeated, or prolonged seizures
10. Failure to respond to treatment for an acute problem/symptom
11. Acute change in urine output to less than 50ml in 4 hours

The primary responders of the Rapid Response Team include a Critical Care Nurse and a Respiratory Therapist. The nurse administrator will facilitate bed placement whenever needed. Their services are available 24 hours a day/7 days a week to inpatients in designated areas. Documentation will be maintained for all RRT activations.

Adverse Event Reporting

An adverse event is defined as "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research" (OHRP, DHHS, 2007).

The attending physician and NASA Flight Analogs Project Scientist are responsible for monitoring subject health, safety and well being throughout the study. Should an untoward event occur, the attending physician and NASA Flight Analogs Project Scientist will determine whether or not the event requires reporting to the NASA CPHS and UTMB IRB. Events that are expected and described in the consent form do not require reporting under the HHS regulations 45 CFR part 46.103(a) and 46.103(b)(5) (OHRP, DHHS, 2007). However, any serious expected event will be reported. To determine whether an adverse event is an unanticipated problem that must be reported, attending physician and NASA Flight Analogs Project Scientist will determine whether or not the adverse event 1) was unexpected, 2) related or possibly related to participation in the research, and 3) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized (OHRP, DHHS, 2007). In cases where there is difficulty determining whether or not an adverse event is reportable, the DSMB will be consulted to assist in this process.

Once the determination is made to report the event, it will be reported within 24 hours of occurrence or recognition. Adverse events are reported via e-mail to the NASA CPHS, UTMB IRB and ITS-CRC through the Research Subject Advocate. As per UTMB IRB guidelines, detailed, written report will be submitted within 10 working days to the UTMB IRB and a copy will go to the ITS-CRC Research Subject Advocate. Aggregate reports of adverse events will be prepared and submitted with the annual protocol review to the NASA CPHS, UTMB IRB and ITS-CRC.

Subject Reimbursement

At the DSMB meeting on December 10, 2010, the board asked that the Flight Analogs Project examine "a reimbursement scheme that would make it less likely for subjects to fail to report symptoms because of a perceived possible loss of reimbursement for future time in the trial." After investigating options with the

NASA CPHS and UTMB IRB, the Flight Analogs Project posed the options to the DSM. Discussion among the DSMB members yielded the following solution.

> Subjects will be reimbursed for their time and if released from the study for any reason, compensation will be prorated to that point. Subjects released for medical reasons will be reimbursed up to that point, and then provided medical care. Subjects released from the study due to ocular issues will be asked to remain on the unit for observation and medically indicated treatment.

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APPENDIX: Review of Systems Questionnaire

Test Subject Review of Systems **Test Subject Number** _____

Date_____ **Bed rest study day** _____

During the past _____, have you experienced any of the following symptoms?
(day/week)

Headache	☐**Yes**	☐**No**
Sinus congestion	☐**Yes**	☐**No**
Runny nose	☐**Yes**	☐**No**
Difficulty swallowing	☐**Yes**	☐**No**
Changes in taste or smell sensation	☐**Yes**	☐**No**
Changes in appetite	☐**Yes**	☐**No**
Brief dimming (graying) of vision	☐**Yes**	☐**No**
Decreased or blurry vision	☐**Yes**	☐**No**
Double vision	☐**Yes**	☐**No**
Unusual flashes of light	☐**Yes**	☐**No**
Pain in or around the eye	☐**Yes**	☐**No**
Increased sensitivity to light or sound	☐**Yes**	☐**No**
Difficulty hearing	☐**Yes**	☐**No**
Ringing or pulsating sounds in your ears	☐**Yes**	☐**No**
Vertigo or dizziness	☐**Yes**	☐**No**
Joint Pain or stiffness	☐**Yes**	☐**No**
Pain in your: Neck	☐**Yes**	☐**No**
Shoulder	☐**Yes**	☐**No**
Arm	☐**Yes**	☐**No**
Back	☐**Yes**	☐**No**
Legs	☐**Yes**	☐**No**
Feet	☐**Yes**	☐**No**
Numbness or weakness in any part of your body	☐**Yes**	☐**No**
Chest discomfort	☐**Yes**	☐**No**
Rapid heart rate	☐**Yes**	☐**No**
Difficulty breathing	☐**Yes**	☐**No**
Rashes or other skin changes	☐**Yes**	☐**No**
Itching	☐**Yes**	☐**No**
Nausea or increased stomach awareness	☐**Yes**	☐**No**
Constipation	☐**Yes**	☐**No**
Difficulty or pain with Urination	☐**Yes**	☐**No**
Bloating or abdominal cramping	☐**Yes**	☐**No**
Diarrhea	☐**Yes**	☐**No**
Sleep disturbances	☐**Yes**	☐**No**
Increased fatigue	☐**Yes**	☐**No**
Difficulty concentrating	☐**Yes**	☐**No**
Mood changes	☐**Yes**	☐**No**
Any other new or unusual symptoms	☐**Yes**	☐**No**

Nursing: For any positive responses, please document symptom details, including dates, duration, context, and severity on the back of this sheet.

☐ **Check here if information is entered on the back of this form.**