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Project Title:	Comparison of Continuous Non-Invasive and Invasive Intracranial Pressure Measurement		
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Human Research Program Risks:	(1) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)		
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Contact Monitor:		**Contact Phone:**	
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COI Name (Institution):	Voss, Susan (Smith College) Hamilton, Doug (Wyle Integrated Sciences and Engineering Group)		
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	Introduction: Recently, astronauts in long-duration spaceflight have been found to have a syndrome consisting of swelling of the optic nerve, impaired vision, and elevated cerebrospinal fluid pressure (also known as intracranial pressure [ICP]) via lumbar puncture (LP), which is similar to the syndrome of idiopathic intracranial hypertension (IIH). It is not possible to perform an LP on astronauts in space. Noninvasive methods of estimating ICP exist but have not been tested against continuous ICP methods in a patient cohort that is physiologically similar to that of astronauts. Accurately determining the presence or absence of ICP elevation during spaceflight is critical (1) for determining if ICP elevation causes these abnormalities, thus identifying the need for appropriate prevention and treatment and (2) for monitoring astronauts during spaceflight to determine if they are at risk for eye abnormalities and visual impairment because of ICP elevation. Primary Objective: Determine the validity, reliability, accuracy, and precision of two noninvasive methods of ICP		

Task Description:	measurement (tympanic membrane displacement [TMD, Marchbanks Measurements Systems, UK] and distortion product otoacoustic emissions [DPOAE]) in comparison to a reference standard, invasive ICP measurement, in human subjects undergoing diagnostic ICP monitoring. Methods: This is a prospective research protocol involving human patients. Eligibility criteria include (1) adults ages 18-65 years, (2) clinically indicated need for continuous ICP monitoring for the diagnosis of hydrocephalus, IIH, or shunt malfunction, or (3) clinically indicated need for CSF-infusion testing for the diagnosis of hydrocephalus or IIH. Invasive ICP methods include (1) spinal catheter insertion and fluid-coupled external transducers for patients with hydrocephalus, IIH, (2) insertion of a 25-gauge needle into the shunt reservoir and fluid-coupled external transducers for patients with shunt malfunction, and (3) CSF-infusion testing, which will use a standardized automated system, Likvor Celda System (http://www.likvor.com) that has been validated in clinical use in Sweden. Noninvasive ICP methods include TMD method and DPOAE. Protocols: (1) Continuous ICP Monitoring. Simultaneous measurement of invasive and noninvasive ICP will be made in the following conditions: (a) Awake in the supine, sitting, standing, and 6-degree head-down position, (b) Asleep in the patient's preferred position, which will be either supine or with slight elevation of the head of the bed. Data will be analyzed in intervals that correspond to the shortest amount of time necessary for each noninvasive method to provide reliable data. (2) CSF-Infusion Testing. CSF-infusion testing will use the continuous-pressure method, in which ICP is regulated to 6 predetermined pressure levels in steps of 3 mmHg. Noninvasive ICP will be measured at each pressure level, allowing controlled, identical pressure range for evaluation in each patient. Significance: This proposal specifically addresses NASA's High Priority Research Area in Visual Impairment and Intracranial Pressure. The validation of noninvasive ICP methods is of utmost importance for the goal of measuring ICP in spaceflight, which is essential for the health and safety of astronauts in long-duration spaceflight. The noninvasive methods must be shown to be accurate over the pressure ranges expected in normal individuals (0-15 mmHg) and in those with an IIH-like presentation post-flight (15-40 mmHg). Without validation in the physiologic range expected in normal individuals and those with intracranial hypertension, noninvasive ICP measurement methods cannot be selected for advancement through Technology Readiness Levels to be designed for use in an exploration mission (TRL-6).
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The outcome of this research program will have widespread benefits and Earth-based applications. The validation of reliable, portable, noninvasive methods of ICP measurement will dramatically change evaluation and management practices for thousands of children, adults, and elderly who have chronic disorders of CSF circulation, including idiopathic intracranial hypertension (IIH), hydrocephalus, shunt malfunction, and spontaneous intracranial hypotension. Currently, only invasive methods exist for accurately assessing whether ICP is normal or abnormal in these patients; however, their invasive nature limits their usage. As a result, many patients are managed with woefully imprecise methods, such as CT or MRI scans, assessment of clinical signs and symptoms, or empiric decisions to insert, remove, or revise shunts. Noninvasive ICP measurement will provide rapid reassurance to patients, parents, and physicians when a child with hydrocephalus becomes ill and it must rapidly be determined whether the illness represents shunt obstruction with elevated ICP or merely a systemic illness such as a cold or the flu that can cause similar symptoms. In the elderly with shunts for normal pressure hydrocephalus, the ability to routinely and noninvasively assess ICP before and after shunt surgery will offer reassurance that the shunt is functioning and that the patient is adequately treated. Alternately, noninvasive ICP measurement can help to determine if a shunt pressure setting is too low, putting the patient at risk for overdrainage with subdural fluid collections or hematomas. Additionally, patients with acute ICP elevation, such as those with stroke, brain tumor, intracerebral hemorrhage, or traumatic brain injury, would benefit from the rapid availability of noninvasive ICP measurement.
Task Progress:	In our application, we indicated that Year 1 would be used for equipment acquisition, training of investigators in use of the equipment, finalization of the protocols, creation of case report forms, submission of IRB applications, and submission of IDE applications. Equipment Acquisition: We obtained 1) Grason-Stadler GSI 39 Auto Tymp tympanometer, 2) Mimosa Acoustics HearID Auditory Diagnostic System to measure DPOAE, and 3) Marchbanks MMS-12 TMD Cerebral and Cochlear Fluid Pressure Analyzer, which was not received until June 11, 2013. Per discussions with NSBRI, we have purchased a second Marchbanks MMS-12 headset and a second ER10 probe for the Mimosa System for backup purposes. IRB Application, Finalization of Protocols, and Creation of Case Report Forms: We obtained IRB determination of nonsignificant risk status for the Marchbanks MMS-12, and IRB approval for the Continuous ICP Monitoring Subprotocol. A protocol to test the noninvasive devices on healthy human subjects is pending IRB approval. All protocols have been finalized and all case report forms have been created and are being edited. The continuous ICP monitoring subprotocol was registered (NCT01863381) on the ClinicalTrials.gov (http://clinicaltrials.gov/) website, and a notice was placed on our website. We are planning to place notices on the Hydrocephalus Association and the Intracranial Hypertension Research Foundation websites. Subject Recruitment: Because of delays in equipment acquisition, and the addition of a protocol to test the noninvasive devices on healthy human subjects, subject recruitment, which was expected to begin at Month 9, has not begun as of the time of this report. Investigator Training: Investigators met in Baltimore on June 17, 2013 to train in the use of TMD and DPOAE, which included a site visit by Robert Marchbanks. Training in Likvor Celda CSF infusion testing is scheduled for September 17-21, 2013 at the University of Umeå Hospital. IDE Application to the FDA for the Likvor CELDA: The application process has taken longer than anticipated. A 1470 page IDE application was submitted and after a teleconference with FDA staff, an amended IDE was submitted. We received a Decision Letter on July 22, 2013 indicating disapproval of the application pending response to numerous technical concerns. After extensive discussion with Likvor, we concluded that we cannot address the FDA's concerns within the time frame of the grant. With NSBRI input, we have revised our plan so that the PI will travel to Umea, Sweden to perform the TMD and DPOAE noninvasive ICP on subjects who are undergoing the CELDA infusion for

	clinical purposes.
Bibliography Type:	Description: (Last Updated: 08/24/2020)