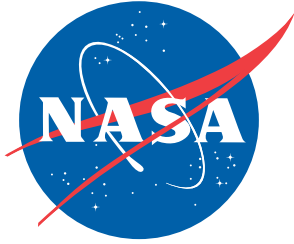


NASA/TM-2011-217062/Volume I
NESC-RP-10-00659



In-Suit Light Exercise (ISLE) Prebreathe Protocol Peer Review Assessment

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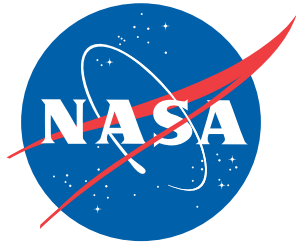
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National Aeronautics and
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**In-Suit Light Exercise (ISLE)
Prebreathe Protocol Peer Review Assessment
Volume I**

NRB Review Date: December 14, 2010

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Report Approval and Revision History

Approval and Document Revision History

NOTE: This document was approved at the December 14, 2010, NRB. This document was submitted to the NESC Director on January 26, 2011, for configuration control.

Approved Version:	Original Signature on File	1/27/11
1.0	NESC Director	Date

Version	Description of Revision	Office of Primary Responsibility	Effective Date
1.0	Initial Release	Mr. Timothy Brady, NESC Systems Engineering Office, Johnson Space Center	12/14/10



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Volume I: Technical Assessment Report

1.0 Notification and Authorization


Dr. Michael Duncan of the Johnson Space Center (JSC) Space and Life Sciences Directorate (SLSD) requested NASA Engineering and Safety Center (NESC) support for an independent peer review of the In-Suit Light Exercise (ISLE) Prebreathe Protocol for use prior to extravehicular activity (EVA) on the International Space Station (ISS).

NESC Director Ralph Roe approved an NESC out-of-board activity on August 11, 2010. Mr. Tim Brady, JSC, was selected as the assessment lead. An initial summary for this assessment was presented at the August 12, 2010, NESC Review Board (NRB) meeting. The NRB approved the assessment plan on September 16, 2010.

The ISLE peer review convened on October 14, 2010, to examine the physiological, modeling, and operations data related to the ISLE Prebreathe Protocol and assess the decompression sickness (DCS) risk regarding the use of the protocol. Following the presentation of data, a Review Committee conducted 4 hours of deliberations on October 14, 2010, and later continued the deliberations between the voting Committee members through email.

The Review Committee produced a final report (see Appendix C) which was submitted to Dr. James Polk of JSC SLSD and Mr. Brady on November 9, 2010. This NESC report integrates the Review Committee's final report with additional background material.

The key stakeholders for this assessment are Dr. Polk and Mr. Derek Hassmann of the JSC Flight Directors Office.

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2.0 Signature Page

Submitted by:

Team Signature Page on File – 2/22/11


Mr. Timothy K. Brady

Date

Dr. James D. Polk


Date

Signatories declare the findings and observations compiled in the report are factually based from data extracted from Program/Project documents, contractor reports, and open literature, and/or generated from independently conducted tests, analysis, and inspections.

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3.0 List of Team Members, Ex Officio Members, and Others

Name	Discipline	Organization
ISLE Prebreathe Protocol Peer Review Committee (Non-voting)		
J.D. Polk	Chief, Space Medicine Division, SLSD	JSC
Tim Brady	NESC Lead	NESC SEO
Pat Forrester	NESC Astronaut Representative	Astronaut Office
Nigel Packham	Safety and Mission Assurance	JSC
ISLE Prebreathe Protocol Peer Review Committee (Voting)		
Caroline Fife	Consultant	The University of Texas Health Science Center at Houston
Bruce Butler	Consultant	The University of Texas Health Science Center at Houston
Ralph Frankowski	Professor of Biostatistics	The University of Texas School of Public Health
Richard Jennings	Consultant	The University of Texas Medical Branch
Richard Moon	Consultant	Duke University Medical Center
Paul Sheffield	Consultant	International ATMO, Inc.
Keith Van Meter	Consultant	Keith Van Meter and Associates
Presenters		
Derek Hassmann	Flight Director	JSC
Joe Dervay	Lead EVA Flight Surgeon, Medical Operations	JSC
Mike Gernhardt	Astronaut Office	JSC
Megan Murphey	EVA Operations Branch	JSC
Johnny Conkin	Biomedical Research and Operations Branch	JSC
Alan Feiveson	Biomedical Research and Operations Branch	JSC
Administrative Support		
Pam Throckmorton	MTSO Program Analyst	LaRC
Melinda Meredith	Project Coordinator	LaRC/ATK
Carolyn Snare	Technical Writer	LaRC/ATK


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4.0 Executive Summary

The atmospheric pressure of the International Space Station (ISS) is 14.7 pounds per square inch (psi), or sea level, whereas the pressure inside the suits used for extravehicular activity (EVA) is 4.3 psi. Thus the performance of EVA by National Aeronautics and Space Administration (NASA) astronauts involves the risk of decompression sickness (DCS). This risk has been mitigated by the use of oxygen (O₂) “prebreathe” to effectively wash out tissue nitrogen (N₂) prior to each EVA. The family of prebreathe protocols developed for the demanding EVA schedule of ISS construction has performed well. None of the 331 EVAs conducted from the Space Shuttle Orbiter and the ISS reported DCS.

Now that the Space Shuttle Program (SSP) is being retired, high-pressure oxygen will become a limited resource. The In-Suit Light Exercise (ISLE) Prebreathe Protocol offers several potential benefits including its potential to save 6 pounds (lb) of oxygen per EVA, and that it does not require astronaut isolation in the air lock overnight as does the “Campout” Prebreathe Protocol. In ground-based testing of ISLE, the measured incidence of DCS was 4.3%, which met the accept criteria at the 95% confidence interval (CI). Although the Grade IV venous gas emboli (VGE) incidence of 16.7% was within the accept criterion of ≤ 20%, the upper confidence limit (CL) failed to meet the 95% CI. In addition, questions existed as to whether the “light exercise” requirement could be validated by perceived exertion or necessitated confirmation by the O₂ sensor in the extravehicular mobility unit (EMU).

At the request of the NESC, the peer review convened on October 14, 2010. The major recommendation of the Review Committee was that the ISLE protocol was acceptable for operational use as a prebreathe option prior to EVA. Furthermore, since the necessary O₂ consumption rate of 6.8 ml·kg⁻¹·min⁻¹ is marginally above a resting rate and is virtually guaranteed by the nature of normal pre-EVA tasks, the use of the EMU suit O₂ sensor is not necessary to determine whether an adequate metabolic rate has been achieved. However, the collection of O₂ sensor readings may be useful for research.

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5.0 Assessment Plan

The JSC SLSD requested NESC support for a peer review of the ISLE Prebreathe Protocol prior to EVA for use on the ISS. The ISLE Protocol involves in-suit light exercise during a 1.5-hour prebreathe period. The ISLE Protocol was developed based on the protocol tested on the ground in the Phase V-5 series of the Prebreathe Reduction Program (PRP). Ground trials of the Phase V-5 Protocol are complete and the peer review was requested to review the ISLE Protocol in addition to the multi-level board approval process prior to use on orbit. The Committee reviewed the physiological, modeling, test subject data, and operations associated with this Protocol and risk associated with DCS.

A peer review panel was originally formed under NESC Request 05-032-E (05-00137) in May 2005 to review the Campout Protocol prior to its use on ISS. A majority of the medical expert panelists from the 2005 review participated in this activity. For the ISLE Prebreathe Protocol assessment, a representative from the JSC Safety and Mission Assurance (S&MA) organization and the NESC astronaut representative were added to the Review Committee.


6.0 Report and Appendices Overview

The appendices to this NESC final report provide background material related to the ISLE Prebreathe Protocol and include presentations made during the October 14, 2010, ISLE Prebreathe Protocol peer review. See Volume II for the appendices.

7.0 ISLE Prebreathe Protocol Peer Review Team Consultation Plan

The assessment plan established the ISLE Prebreathe Protocol Review within the NESC. It defined the mission, responsibilities, membership, and conduct of operations for this assessment. This assessment was initiated out of board by NESC Director Ralph Roe. NESC's mission is to perform value-added independent testing, analysis, and assessments of NASA projects to ensure safety and mission success. The objective of this assessment was to review the physiological, modeling, and operations data related to DCS risk regarding the use of the ISLE Prebreathe Protocol. Specific questions were posed to the Review Committee in the Charge to the Committee (See Section 8.0), with the findings and recommendations to be documented in a written report and outbriefed to the NRB and identified stakeholders.

The ISLE Prebreathe Protocol Review Committee presentation activities on October 14, 2010, were led by Mr. Tim Brady. Dr. Caroline Fife from the University of Texas Health Science Center, Houston, was tasked with assembling the independent voting members of the Committee. Members of JSC SLSD and the EVA operations community identified the critical areas of information necessary for the Committee briefing. Informational materials were circulated to the voting and non-voting members prior to the meeting date. Presentations were

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made during the meeting at the Center for Advanced Space Studies in Houston, Texas, to educate the Review Committee about the background of ISLE Prebreathe Protocol development, physiology of altitude DCS, statistical methods for development and analysis, modeling data, and aspects of operations which were pertinent to this review (e.g., available equipment, physical limitations, etc.). Results from the Phase V-5 ground test were extensively reviewed. The Phase V-5¹ ground test protocol was representative of the ISLE Prebreathe Protocol which would be operationally implemented on ISS.

Presenters included Mr. Derek Hassmann who presented the Flight Director operations perspective, Dr. Joe Dervay who presented EVA prebreathe protocol history, Dr. Mike Gernhardt who presented the research summary, Ms. Megan Murphey who presented the operational prebreathe timelines, Dr. Johnny Conkin and Dr. Al Feiveson who together presented modeling methods, and Mr. Tim Brady who presented the Charge to the Review Committee.


After the Charge was presented by Mr. Brady, the Committee was allowed to deliberate privately with the input of the non-voting members under the supervision of Mr. Brady, Dr. Nigel Packham, and Col. Pat Forrester, NESC Chief Astronaut. The EVA Integrated Product Team (IPT) presenters remained available during Committee deliberations to answer questions.

Analysis Techniques Used

The Review Committee consisted of seven voting members (Dr. Fife, Dr. Richard Jennings, Dr. Bruce Butler, Dr. Ralph Frankowski, Dr. Paul Sheffield, Dr. Richard Moon, and Dr. Keith Van Meter) and four non-voting members (Mr. Brady, Dr. Polk, Dr. Packham, and Col. Forrester).

The Review Committee deliberated for approximately 4 hours. The Committee requested Dr. Frankowski to estimate the number of subjects which would have been necessary to reach the 95% CI for the Phase V-5 accept/reject criteria. Dr. Gernhardt answered questions posed by the Committee via telephone during their deliberations. Deliberations continued after the meeting through email. Key statements were crafted by the members and emailed to the voting members who voted by email using a “Delphi” approach. Draft statements were revised until there was unanimous agreement by the voting members. A draft report prepared by Dr. Fife was circulated by email for review. Dr. Polk and Mr. Brady reviewed the report with regard to the accuracy of the background information and the NESC procedural details. The Committee’s final report was submitted to Dr. Polk and Mr. Brady on November 9, 2010. The ISLE Prebreathe Protocol Peer Review final report was presented to the NRB for approval on December 14, 2010.

¹ Phase V-5 refers to the ISLE ground prebreathe protocol test in the PRP discussed in Section 9.4.

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8.0 The Charge to the ISLE Prebreathe Protocol Peer Review Committee

- Is the ISS ISLE Prebreathe Protocol acceptable for operational use with the O₂ tank pressure transducer readings as guidance for controlling the crew metabolic rate during the light exercise period?
- Is the ISS ISLE Prebreathe Protocol acceptable for operational use using ratings of perceived exertion (RPE) of 7 or greater as a control to insure adequate metabolic rate has been achieved during the light exercise period?
- What, if any, additional controls would be recommended for implementation of the ISLE Prebreathe Protocol for routine operational use on ISS?


9.0 ISLE Prebreathe Protocol Background and the Statement of the Problem

9.1 Background of Prebreathe Testing

The testing of prebreathe protocols has evolved since the 1970s. A variety of methods has been used including ground-based testing of specific prebreathe protocols with the later addition of “adynamia” (no ambulation) simulations, mathematical modeling based on accumulated data from closely related studies, and multi-center prospective trials to evaluate specific prebreathe techniques. NASA’s goal is not the performance of DCS research. The primary goal is the development of safe and effective DCS countermeasures for EVA. A secondary goal is a better understanding of prebreathe mechanisms. Thus, these prospective trials have been designed with operational considerations in mind and with carefully defined *a priori* accept/reject criteria.

Early prebreathe protocol development focused only on delivering acceptable/effective countermeasures. Later development focused on increased efficiency and improved scientific understanding of countermeasure mechanisms. The evolution of the overarching goals of prebreathe research is reflected in the changing design of the trials. Early in the SSP, Dr. James Waligora tested many prebreathe protocols (3, 3.5, and 4 hours) in which the DCS incidence ranged from 20–36%. Exercise simulated the arm movement of the crank on the Space Shuttle Orbiter payload doors and other Orbiter contingency tasks. In testing the 4-hour “In-suit” Prebreathe Protocol and the 1-hour, 10.2 psi “staged decompression,” specific “R” values were identified for acceptable tissue tensions, and “reject” criteria were identified (e.g., “Grade 3 DCS, any Type II, pain limiting performance, etc.”). In the 10.2-psi staged decompression prebreathe ground-based tests, a DCS incidence of 23% was observed.

In the late 1990s, the EVA requirements for ISS necessitated prebreathe protocols which were more time and operationally efficient. Research that enabled the PRP to proceed included the recognition that ground-based microgravity simulation was an important experimental variable

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and the discovery that exercise significantly enhances N₂ off-gassing (e.g., 10 minutes of exercise at 75% O₂ intake (VO₂) peak during a 1-hour prebreathe protocol was equivalent to a 4-hour resting O₂ prebreathe). The goal was to reduce the prebreathe time by 50% over the 4-hour protocol while maintaining or increasing the safety margins to DCS and to certify this protocol in time for the installation of the ISS joint airlock. A 2-hour exercise prebreathe protocol for ISS was developed by 1999. During that period, the EVA culture was transformed to a “diving environment” mentality with a clear DCS treatment and disposition policy which did not penalize astronauts for reporting DCS should it occur. Improved on-orbit treatment protocols were developed which allowed in-suit recompression breathing O₂ (4.3–8 psi over ambient).


Over the years, four prebreathe protocols have been developed which allow flexibility similar to that used in diving. These protocols have had extensive use during EVAs on the Space Shuttle Orbiter and on ISS.

- 3.5 hour In-Suit Prebreathe; 4.0 hour In-Suit Prebreathe
- 10.2 psi Staged Prebreathe
- 2-hour Cycle Ergometer with Vibration Isolation and Stabilization (CEVIS) Exercise Protocol
- ISS Airlock Campout Prebreathe Protocol

The prebreathe protocol selected for each EVA is based on operational, technological, and astronaut preference factors. There has been one instance in which an unintended break in Campout Protocol necessitated moving to the Exercise Prebreathe Protocol. On this occasion, automatic repressurization of the air lock occurred as a result of a false depressurization alarm. Thus, the availability of multiple prebreathe options has provided operational flexibility.

9.2 EVA Protocol Metrics (as of 17 August 2010)

- 3.5 hour In-Suit Prebreathe
 - 2 person-EVA in one use
- 4.0 hour In-Suit Prebreathe
 - 4 person-EVAs in two uses
- 10.2 psi Staged Prebreathe
 - 151 person-EVAs in 75 uses
- CEVIS Exercise Prebreathe
 - 38 person-EVAs in 19 uses
- Campout Prebreathe
 - 136 person-EVAs in 68 uses

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In 331 EVAs there have been no reported cases of DCS. Discussions with astronauts and the established policy allowing return to EVA status if DCS was reported (assuming certain conditions are met) indicate that these statistics do not reflect a lack of reporting but indeed, the absence to date of recognized DCS symptoms related to EVA over the past 10 years. Possible reasons for this are discussed below.

Initially, “acceptable risk” in ground-based prebreathe protocol development was defined by the following parameters:

The highest DCS risk consistent with a 95% probability that two of three members would always be available for EVA was 21%, and that during testing, DCS and Grade IV VGE incidence would be below the threshold for any reported case of Type II DCS.

Acceptable DCS risks were further reduced to account for related medical factors such as an on-orbit treatment delay of 30–45 minutes for re-pressurization, and the presence of a patent foramen ovale (PFO), which might result in neurological symptoms due to arterialized venous gas. To address this issue, experimental ground-based protocol design further specified that Type I DCS remain at a threshold below which no cases of Type II DCS have been reported in the literature. In 244 tests with 7,692 exercising subjects, neurological DCS is not observed until the incidence of Type I DCS exceeds 15% [ref. 1].


Thus, for the Phase V-5 ground test protocol, the accept limit was a DCS incidence $\leq 15\%$ at 95% CL and Grade IV VGE $\leq 20\%$ at 95% CL. The reject limit was a DCS incidence $> 15\%$ at 70% CL and Grade IV VGE $> 20\%$ at 70% CL. The protocol was also rejected if there was a case of DCS classified as Type II.

It must be noted that the *a priori* accept/reject criteria established in testing protocols for ISS were far more rigid than those used for testing the SSP prebreathe protocols. The Review Committee felt the accept/reject limits for the Phase V-5 ground trial were more conservative than any previous EVA prebreathe trial.

9.3 Statement of the Problem

In the Phase V-5 ground-based testing, the measured incidence of DCS with ISLE was 4.3% (two cases of Type I DCS in 47 trials). The upper one-sided exact binomial CL for the true incidence of DCS was 12.8%. There were no cases of Type II DCS with the Phase V-5 ground trial. This met the accept criteria of $\leq 15\%$ DCS at 95% CL.

In ground-based testing, the measured incidence of Grade IV VGE was 16.7% (eight cases of Grade IV VGE in 48 trials). The upper 95% one-sided exact binomial CL for the true incidence of Grade IV VGE was 28.1%. Although the point estimate of VGE incidence of 16.7% is within the accept criterion of Grade IV VGE $\leq 20\%$, the upper CL fails to meet the 95% CL requirement. The upper 64% CL for Grade IV VGE was 19.96%. Thus, to qualify for

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acceptance, the 95% CI requirement would have to be reduced to a 64% CI requirement. Alternatively, these results could be examined from a Bayesian perspective wherein a probability statement could be made about P(VGE) given the experimental results of eight cases in 48 trials. Using a (conservative) uniform prior for P(VGE), the posterior distribution of P(VGE) given the data is distributed as Beta (9, 41) distribution. With this posterior distribution, the probability that P(VGE) exceeds 20% is about 33.2% [ref. 2]. Despite the failure of Grade IV incidence to meet the 95% CI requirement for acceptance, the Bioastronautics EVA-IPT unanimously agreed that the Phase V-5 ISLE Prebreathe Protocol should move forward for consideration for operational use.

The Review Committee assessed the operational issues that are driving ISLE consideration even though ISLE did not meet accept criterion at the 95% CI. For ISS-based EVA, the Campout Protocol has worked well but does have the logistical issue of isolation. The ISLE Protocol has some advantage over the Exercise Prebreathe Protocol in that the CEVIS exercise bicycle is not necessary and it provides an alternative for those who find the prebreathe mask uncomfortable. However, high-pressure O₂ will become a limited resource once resupply from the Space Shuttle Orbiters is no longer available. For some years, until an engineering solution is developed and delivered to ISS, there will be no way to recharge the high-pressure O₂ supply. Post SSP retirement, support of ISS could require eight EVAs per year, although a realistic requirement is one to two EVAs per year (see Appendix D).

The Review Committee felt the ISLE Prebreathe Protocol has the potential to offer several benefits, including:

- Is expected to save 6 lb of O₂ per EVA
- Does not require astronaut isolation in the air lock overnight compared to the Campout Protocol
- Requires less crew time on prebreathe hose mask (which can be uncomfortable and difficult to use)
- Could be a better down-mode option if the Campout Protocol is broken (which has occurred one time to date)
- Allows astronauts to “get out the door” 13–30 minutes earlier than CEVIS Exercise Protocol
- Diminishes the “rushing” to prepare for campout
- Does not require crew to either do a bathroom break on their 120-ft prebreathe hose or use piddle packs
- Does not require VO₂ peak testing as exercise prescription is based on weight only (6.8 ml·kg⁻¹·min⁻¹)
- Is a simpler procedure overall than CEVIS Exercise Protocol

ISLE Prebreathe Protocol has some potential operational disadvantages and/or challenges, including:

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- Astronauts would “get out the door” about 60 minutes later than Campout Protocol
- Requires about 100-minute in-suit prebreathe time versus 50 minutes in-suit on Campout Protocol
- Presupposes a certain (minimal) level of exercise in-suit during the prebreathe (see Section 9.7), which could use O₂-sensor readings as a general, non-required guide of activity

9.4 The Development of ISLE Prebreathe Protocol

The PRP was initiated in 1997 with the objective to develop, test, certify, and implement a 2-hour Prebreathe Protocol for EVA in time for first use of the ISS joint airlock [ref. 4]. The PRP ground test study was reviewed by an external expert committee chaired by Dr. C.J. Lambersten and the accept/reject criteria were more conservative than any previous EVA prebreathe trial. The PRP study was a sequential, multi-center trial, utilizing informed consenting subjects representative of the astronaut population in terms of age, gender, fitness, and percentage of body fat.

The mission driver was a 95% probability that two of three crew members would be available for EVA throughout the ISS Program, combined with additional medical/operational considerations, which resulted in the following accept/reject limits:

- Accept: DCS < 15% and Grade IV VGE < 20%, at 95% CL
- Reject: DCS > 15% or Grade IV VGE > 20%, 70% C, or any case of Type II DCS

There was a 50-trial minimum to control type II error to less than 1%. The research plan anticipated testing up to four protocol options. Previous Phase V in-suit exercise protocols did not incorporate a 10.2-psi depress/repress, and PRP data (all protocols) showed that the 10.2-psi depress/repress significantly reduced DCS and VGE. Thus, a 10.2-psi depress/repress was added to the Phase V-5 Protocol.

Table 9.4-1 provides the PRP summary results.


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Table 9.4-1. Summary of Results from PRP Protocol Series

Protocol	n	%DCS (n)	%VGE (n)	%GIV VGE (n)
I	47	19.1 (9)	48.9 (23)	4.2 (2)
II	45	0 (0)	31.1 (14)	6.6 (3)
III	9	22.2 (2)*	11.1 (1)	11.1 (1)
IV	56	14.3 (8)	41.0 (23)	12.5 (7)
V-1	9	33.3 (3)	55.5 (5)	22.2 (2)
V-2	3	33.3 (1)*	100.0 (3)	66.6 (2)
V-3	48	14.6 (7)	52.1 (25)	10.4 (5)
V-4	6	50.0 (3)	50.0 (3)	16.6 (1)
V-5	48**	4.2 (2)	29.2 (14)	16.6 (8)

*Includes one case of Type II DCS

**Based on 48 acceptable trials for Grade IV VGE and 47 trials for DCS

The Phase V-5 Protocol consists of 60 minutes of O₂ on mask while performing EVA preparations followed by a 10.2-psi depress (light exercise at 5.8 ml·kg⁻¹·min⁻¹) on enriched air (0.265% O₂). This is followed by a 30-minute suit donning at 10.2 psi, and then 50 minutes of in-suit light activity (6.8 ml·kg⁻¹·min⁻¹), which is equivalent to walking a mile in 70 minutes, breathing O₂. It must be noted that this degree of exercise can be achieved with minimal effort. There is a final 50-minute in-suit prebreathe at rest, breathing O₂.

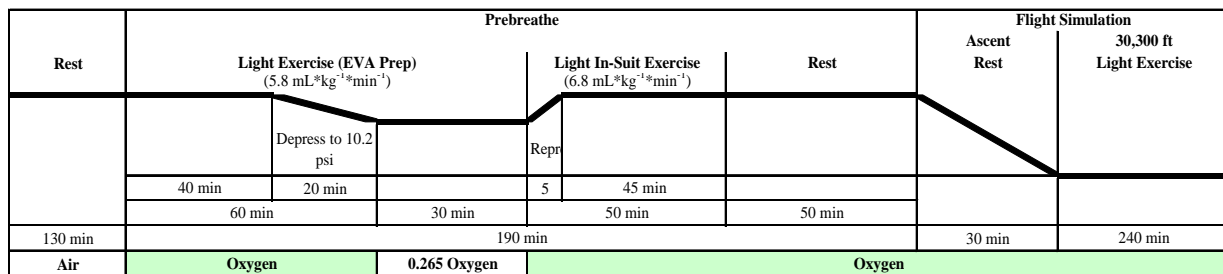



Figure 9.4-1. ISLE Prebreathe Protocol Operational Timeline

The measured incidence of Grade IV VGE was 16.7% (eight cases in 48 trials). This was within the accept criterion of ≤ 20% Grade IV VGE but not at the 95% CL. With the low incidence of DCS in the Phase V-5 Protocol, the increased incidence of Grade IV VGE could not be

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explained based on age, gender, aerobic fitness, total O₂ consumption, total prebreathe time, or relationships between DCS and Grade IV VGE in PRP and NASA historical results.

It is possible that considering only Grade IV VGE and not considering the effects of lower grades or the persistence of decompression stress reduces the sensitivity to differences between protocols. The prebreathe studies included VGE sampling in each 20-minute block of time (epoch) spent at suit pressure (see Appendix F). There was no significant difference (two-sided Fisher exact p-value = 0.56) in the total number of epochs with Grade IV VGE for Phase V-5 and the approved-for-flight Phase II protocols (3.5% and 4.1%, respectively). However, Phase V-5 had significantly lower (two-sided Fisher exact p-value = 0.02) pooled Grade III-IV VGE than Phase II (6.8% versus 10.6%, respectively). Given that combined Grade III and IV VGE are generally associated with statistically increased risk of DCS, it may be that a strict focus on Grade IV VGE only may be a less than comprehensive measure of decompression stress. The duration of VGE grade at the highest grade level within an epoch is not measured, only the notation of maximal VGE grade.

The laboratory protocol does not include the additional safety margin built into the flight protocol including extra prebreathe time during the configuration checks, leak check, purge, and 5-psi suit over-pressurization during crewlock depress. All of these activities add approximately 25 minutes of O₂ prebreathe that was not performed on the Phase V-5 laboratory protocol (i.e., in practical use, astronauts performing the ISLE Prebreathe Protocol would get more O₂ prebreathe than subjects in Phase V-5 ground-based testing).

9.5 Additional Analysis


Drs. Conkin and Feiveson presented supplemental analysis of Phase V-5 data for additional insight into a variety of issues which might impact decision making. These analyses are presented below in the form of questions (Q) and answers (A). The additional analysis presupposes that the VGE data collected over 25 years is “perfect” and contains no DCS diagnostic error, no bias in VGE grading, and that maximum VGE is adequate information.

Q: Does accounting for the frequency of 0 VGE improve the confidence in the observations from V-5?

Since the predictive value (PV) is 98% for “no VGE” and PV is only 32% for “VGE” in current NASA data, the question arose as to whether accounting for Grade 0 VGE could provide more confidence in the observed 4.2% DCS than is suggested by the high Grade IV incidence.

Data were stratified on the presence or absence of symptoms, and used random effects models for P(S|VGE) and P(DCS|VGE, S) to represent test-test variation and estimate standard error of P(DCS) estimate. The final random effects regression equation is as follows:

$$P(\text{DCS}) = (0.0166 \cdot n_0 + 0.188 \cdot n_{123} + 0.514 \cdot n_4) / n$$

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where n_0 is the number of trials within a specific test that were assigned maximum VGE grade of Grade 0, n_{123} is the number of Grade I, II, or III, n_4 is the number of Grade IV, and n is the total number of trials in a specific test. The regression equation provides for a computed $P(\text{DCS})$ for a test given the counts of maximum VGE grades for the trials in the test.

A. The estimated $P(\text{DCS})$ given maximum VGE grade and symptoms is as follows:

test	n	observed DCS	one-side 95% CL*	estimated P(DCS)	one-side 95% CL
V-5	47**	0.042	0.128	0.112	0.171

Q: *What is the likely operational effect of a Type I DCS?*

A literature analysis was presented to gather information regarding the operational impact of Type DCS as a function of the probability of the severity of decompression illness (DCI) which cannot be determined due to stop rules. Data from 1971 in a retrospective analysis of data going back to 1941 converted all symptoms into a scale of 1–4 (something worse than intolerable pain that cleared on descent).

A. If there was a test which gave 30% DCS, then the expectation is that there will be mild categories of DCI and thus a low operational impact.

Q: *What is the estimate of Type I DCS probability given the maximum VGE grades from V-5?*


A. The estimated $P(\text{DCS})$ for Phase V-5 is 11.2% compared to 4.2% from direct count in the ground-based study. The one-sided upper 95% CL is 17.1%. The estimated $P(\text{DCS})$ was 9.1% for Phase II compared to 11.2% for V-5, which is not considered a significant difference.

Q: *What might be the effect of diagnostic error on the data in V-5?*

A. The computed $P(\text{DCS})$ accounting for diagnostic error was 4.5% compared to 4.2% from direct count. Since 44/47 trials had no report of any symptoms, then there was no significant contribution from diagnostic error since one diagnoses DCS based on symptoms. This analysis suggests that after accounting for diagnostic error, the DCS impact of DCS for Phase V-5 is low.

Q: *Why is the observed incidence of DCS difference from ground-based studies?*

A. Astronauts enjoy greater protection from DCS than expected after Campout Prebreathe Protocol, probably through additional operational prebreathe or other protective factors in microgravity (e.g., resolution of bubble micronuclei). There are additional amounts of O_2 which may not be accounted for, and there is additional exercise in the suit.

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- A. There is a fundamental effect of microgravity on the biology of bubble formation and symptom development, the mechanism of which is not understood.

9.6 Issues Relating to the Flight Rule for the ISLE Prebreathe Protocol

Ms. Megan Murphey provided comparisons of the EVA Prebreathe Protocols and the Review Committee assessed the differences between the ISLE, Exercise, Campout, and 4 hour in-suit Prebreathe Protocols with regard to time from post sleep to start of EVA, air lock isolation, mask time, prebreathe time, ISS recommended crew day length, and the number of metal oxide (METOX) cans used.

With regard to METOX can usage, the ISLE Prebreathe Protocol would use about the same number of cans, although there are operational details regarding the re-use of partially spent cans. If the ISLE Protocol is approved, then it would represent another acceptable protocol that can go into the “basket of tools from which to choose.” The decision will be based on operational issues such as O₂ availability, CO₂ canisters, time available, isolation of campout and other factors. The Review Committee felt it is likely that after SSP retirement, the ISLE Protocol will be the preferred prebreathe protocol due to its ability to save high-pressure O₂.

9.7 Issues Relating to the O₂ Tank Pressure Sensor

Dr. Gernhardt presented data suggesting that the drop in the O₂ tank sensor pressure could be used as a guideline to control the ISLE metabolic rate during in-suit prebreathe. However, this method is complicated by the following considerations:

- Thermal transients associated with purge and tank refill
 - Tank pressure drops during purge at 10.2 psi, and at 14.7 psi, tanks are then recharged and thermal cooling causes tank pressure transients.
- As-donned suit leak rate
 - The suits typically leave Earth with leaks of 100 standard cubic centimeters per minute (scm) or less, however as donned the leak rates could be as much as 999 scm and still pass the leak check.
- Tank pressure sensor error and display control module (DCM) rounding error
 - The difference between any two tank pressure readings could have an error of up to 2.6 psi. The DCM could have a rounding error of 0.49 psi.

The Review Committee was provided with a detailed description of engineering work-arounds for these limitations. However, subsequent discussion focused on the On Orbit Engineering Assessment Exercise Prescription Table for an 80-kg subject. ISLE Prebreathe Protocol requires that the in-suit exercise be performed at “light activity” (6.8 ml·kg⁻¹·min⁻¹). This is only slightly more activity than “no exertion at all.” The Review Committee felt data were compelling (see Figure 9.7-1) that it would be virtually impossible for astronauts to fail to perform this level of exertion, simply by remaining awake in the suit during the 50 minutes. Thus, while the O₂



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sensor readings may be noted, they do not appear necessary, and the previously discussed issues with O₂ sensor accuracy argued against relying on it for this purpose.

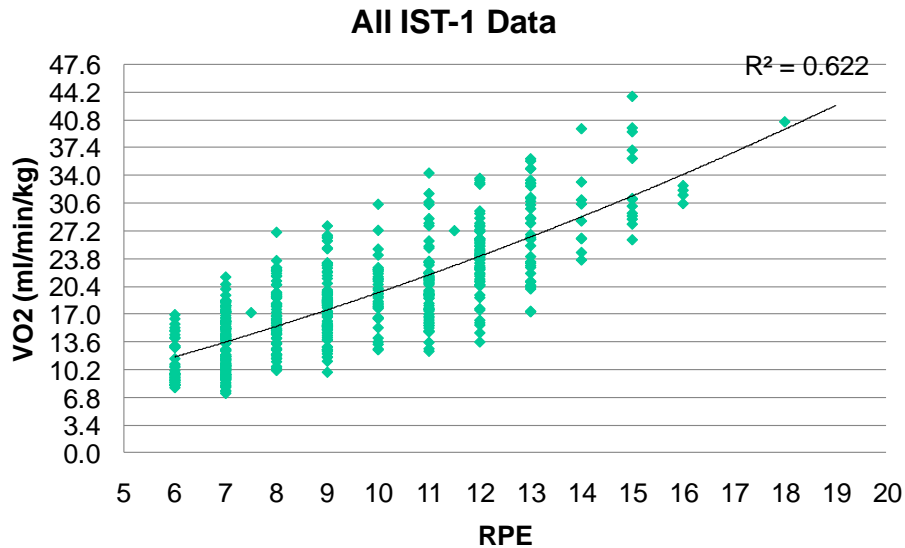


Figure 9.7-1. All I ST-1 Data

The perceived exertion scale seemed a viable and perhaps equally reliable tool for assessing O₂ prebreathe exertion.


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Table 9.7-1. Borg Rate of Perceived Exertion


6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

The crew member must exercise with a rate of perceived exertion (RPE) of 7 (i.e., they are performing some exertion versus an RPE of 6, which is no exertion) to ensure that an adequate exercise intensity was achieved. Further discussion with Dr. Gernhardt revealed that in ground-based testing, the exercise was specifically that of the lower legs and instructing crew members to move their lower legs would be required. Discussion ensued as to whether prescribing a certain number of leg movements was necessary, but Dr. Gernhardt did not feel that this would be necessary to achieve the required exertion.

Data from the suit's O₂ tank sensor pressure drop may provide useful information and thus would be valuable to collect.

10.0 Prior Safety Committee Work

It is important to note that there was no specific ground-based testing of the Campout Prebreathe Protocol. The safety of the Campout Prebreathe Protocol was assessed based on modeling data and information obtained from Phase IV human trials. Phase IV of the exercise prebreathe study was a 2-hour prebreathe with 95 minutes of light exercise, and a 30-minute suit-donning period at 10.2 psia breathing 26.5 % O₂. This ground-based test of Phase IV was nearly identical to the day-of-EVA Campout Prebreathe Protocol, which has the same amount of O₂ prebreathe and the same or slightly more metabolic activity during O₂ prebreathe. Phase IV trials resulted in 14% DCS in 57 subjects, which did not quite meet the accept criteria for ISS EVA, but this incidence

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was lower than the ground tests of the SSP 10.2-psia staged protocol. Compared to Phase IV, the Campout Prebreathe Protocol had an extra hour of O₂ prebreathe, and 8 hours and 40 minutes overnight campout at 10.2 psia. Modeling data suggested that the Campout Protocol would be a safe protocol for EVA, and the Campout Protocol Safety Committee accepted Campout on this basis in 2005 on the argument that it was “analytically more conservative,” even though there was no ground-based testing for validation. The logistic regression model predicted Campout Protocol to have 2.8% DCS (1.2% to 5.9%, 95% CI) based on Dr. Conkin’s work. Nevertheless, there have been no reports of symptoms linked to DCS in 136 person EVAs with 68 uses of the Campout Protocol from the ISS. Thus, it appears that the Campout Protocol in actual EVA use is safer than the model predicts. The possible physiological and operational reasons for this have been previously discussed.


The modeling techniques used to assist in the development of the prebreathe protocols are well known in medicine and physiology, having been used to develop, for example, the cardiac risk score from the Framingham Study data, as well as in pharmaceutical trials, and the techniques of which are accepted by the Food and Drug Administration. It is important to note that, utilizing modeling techniques, the risk of DCS is almost the same for all the prebreathe protocols, and the CIs overlap. There is a tendency to rank the risks within “acceptable risks” even when the differences are small. Given the overlapping CIs, it may be impossible to detect a real difference in risk between the prebreathe protocols, based on modeling.

Analysis of the 95% Bayesian CLs for the risk differences suggests that the SSP ground simulation overestimates the DCS risk in EVA, while ISS ground EVA simulation may provide an accurate prediction of DCS risk (it is possible that the risk of DCS in ISS ground-based trials and EVA are the same). The higher correlation between ISS ground-based trials and predicted DCS risk during EVA may be due to improved ground-based trial design.

11.0 Proposed Solutions

11.1 Going from Evidence to Findings and Recommendations

Since the Prebreathe Safety Committee first met in 2005, a significant focus in clinical medicine has been the methodology by which research data is evaluated for its relevance to clinical practice guidelines. If a practice guideline working group makes a recommendation, how much confidence can be placed in that recommendation? The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group has published extensively on this topic [ref. 3]. Their methods focus on the development of *clinical* practice guidelines based on the results of *medical* research. Thus, these GRADE methodologies are only partially relevant to the process of reviewing *physiological* experiments for the development of NASA *operational* protocols. Clearly the process of evaluating DCS countermeasures is quite different than the process of evaluating practice guidelines for stroke prophylaxis. However, the Review

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Committee has been asked to weigh various types of data, specifically: randomized, controlled trials; predictive models; and “real world practice” (i.e., EVAs); and to synthesize this diverse information in order to make recommendations for prevention of disease (i.e., DCS). Since there are some similarities, the Safety Committee has attempted to utilize some GRADE Working Group techniques to assist the Review Committee in weighing the data presented and establish the level of confidence which can be placed in the Committee’s recommendations.

Like the GRADE Working Group, the Review Committee has used the following definitions:


- **Quality of Evidence:** indicates the extent to which one can be confident that an estimate of effect is correct.
- **Strength of a Recommendation:** indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm.

There are three determinants of the strength of a recommendation: 1) the balance between the desirable and undesirable consequences of the alternative management strategies, on the basis of the best estimates of those consequences, 2) the quality of the evidence, and 3) the values of the stakeholders. When advantages far outweigh the disadvantages, then the strength of a recommendation may increase. If the consequences of the choice are relatively unimportant, even strong evidence supporting a recommendation may not matter. If the consequences are very important, then evidence with less strength may take on a much more prominent role [ref. 3].

11.2 Confidence Interval Calculations

The ground-based DCS data presented for ISLE met the criteria for acceptance of this prebreathe protocol. However when Grade IV VGE data were included, the data did not meet the criteria for acceptance at the predetermined 95% CL for VGE Grade IV incidence $\leq 20\%$ nor did the data meet the criteria for *rejection* of Grade IV VGE $> 20\%$ at the predetermined 70% CL. The lower 70% one-sided exact binomial confidence limit for the true incidence of Grade IV VGE was 13.3%. Thus, the ISLE Protocol could neither be accepted nor rejected based on the accept/reject limits and the reported ground-based V-5 protocol data alone.

There are two main factors that control the width of a confidence interval: 1) sample size, and 2) the true underlying incidence of Grade IV VGE in the study population relative to the criterion value of 20% incidence for accept/reject limits. It is not possible to detect small differences in VGE incidence from 20% without a very large sample size. For example, if the Grade IV VGE incidence is 16.7% in the study population then a sample of at least 336 subjects would be required to satisfy the current VGE 20% acceptance criteria. The implication is that for VGE acceptance small differences between ground-based VGE incidence and the criterion value of 20% require very large samples.

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Sample-size requirements can also be illustrated by recasting the rejection criteria as a traditional test of hypothesis. Suppose the null hypothesis is $H_0: \text{Prb}(\text{Grade IV VGE}) = 20\%$ and the alternative hypothesis is $AH: \text{Prb}(\text{Grade IV VGE}) \geq 25\%$. Then at the 5% level of significance a sample size of 400 would be required to detect the alternative hypothesis with power equal to approximately 75%. If the alternative hypothesis is taken to be that $\text{Prb}(\text{Grade IV VGE}) \geq 30\%$, then a sample size of approximately 100 would have 75% power at the 5% level of significance. Small differences require large samples and large differences require relatively smaller sample sizes. These examples are presented only to suggest that with the extensive amount of VGE data now available it may be time to reconsider the current accept/reject criteria for the incidence of Grade IV VGE.

11.3 Specific Committee Recommendations

11.3.1 Strong Recommendation Based on a Moderate Level of Evidence

An O_2 consumption of $6.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ is barely above resting and is virtually guaranteed by the nature of normal pre-EVA tasks. Thus, light lower body exercise in the suit will ensure an O_2 consumption of at least $6.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ without the use of EMU suit O_2 sensor measurements as part of the ISLE Prebreathe Protocol.

11.3.2 Strong Recommendation Based on a Low Level of Evidence


Even though not necessary to accurately determine whether adequate metabolic rate has been achieved, in-suit O_2 sensor readings collected during the light exercise period may be valuable for future research if collected with very specific and clear-cut objectives.

11.3.3 Strong Recommendation Based on a Moderate Level of Evidence

The ISLE Prebreathe Protocol is acceptable for operational use as a prebreathe option prior to EVA.

11.4 Additional Observations and Recommendations by the Committee

The Review Committee recognizes that, based on its experience, Type I or “pain only bends” goes away with simple repressurization with or without the respiration of O_2 . Were it not to respond to repressurization it would not endanger the life of an astronaut even though it might affect operations. If serious DCS were to occur during EVA, then the most probable mechanism would be via arterialization of VGE. This is because appropriate O_2 prebreathe would eliminate N_2 from well-perfused tissues so that supersaturation would be highly unlikely and thus autochthonous bubble formation in the brain or spinal cord could not occur during EVA. Therefore, the rationale for including VGE in the experimental reject criteria was to protect against the rare, but potentially devastating problem of a serious case of DCS arising from arterialization of these venous bubbles. Thus, the Review Committee deliberates with

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seriousness the question of whether we are in fact, being asked to alter carefully crafted accept/reject criteria *post hoc*. The following observations were made:

- Observation: Over the past 10 years, ground-based accept/reject research criteria have become ever more strict even as data have accumulated demonstrating the complete *absence* of DCS reporting during EVA. The Review Committee raises the issue as to whether JSC ought to revisit the accept/reject criteria of ground-based trials in light of the safety data from EVA.
- Observation: Another issue relates to the possibility whether the identified protocol has too many failure points, adding additional and unpredictable risks. The Exercise Prebreathe Protocol reportedly has 21 potential failure points and the ISLE Prebreathe Protocol has fewer failure points. It is not clear how and if the greater simplicity of the ISLE Protocol impacts operations including lower risk of failure.
- Observation: Phase V-4 was rejected early due to higher rates of DCS. The Review Committee discussed the phenomenon of a “cluster effect” of DCS which has been well described in statistical analyses. Such a cluster could cause the discontinuation of what might turn out to be a potentially viable protocol.
- Observation: The early discontinuation of a trial raised numerous comments regarding ground-based trial design requirements. The Review Committee recognizes the continuous progress of the research group as it has worked to refine and improve methodology. The next logical step may be to adopt a more “pharmaceutical Phase I and Phase II clinical trials” approach in which similar numbers of subjects are enrolled in each protocol even if early cases of DCS occur (unless Type II DCS occurs or the reject criteria are clearly met). This will enable protocols to be evaluated against each other in terms of relative risk. Not only might this further refine our understanding of decompression physiology, but it has distinct advantages in building a more robust model.

Although the explanation remains obscure, there is now a significant body of EVA data that supports the notion that ground-based trials overestimate the likelihood of DCS in microgravity, and by inference, VGE as well. This experience was a factor in the Review Committee’s recommendation to proceed with operational use of the ISLE Prebreathe Protocol. Doppler data in microgravity would be extremely valuable, both to confirm this hypothesis and for use in future predictive studies. Thus, the Committee felt strongly that data regarding VGE on-orbit would be of immense value in interpreting the predictive value of future ground-based protocols.


12.0 Alternate Viewpoints

There were no alternate viewpoints identified during the course of this assessment by the NESC team or the NRB quorum.

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13.0 Acronyms List

AH	Alternative Hypothesis
ATK	Alliant Techsystems, Inc.
CEVIS	Cycle Ergometer with Vibration Isolation and Stabilization
CI	Confidence Interval
CL	Confidence Limit
DCI	Decompression Illness
DCM	Display Control Module
DCS	Decompression Sickness
EMU	Extravehicular Mobility Unit
EVA	Extravehicular Activity
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IPT	Integrated Product Team
ISLE	In-Suit Light Exercise
ISS	International Space Station
JSC	Johnson Space Center
LaRC	Langley Research Center
METOX	Metal Oxide
MOD	Mission Operations Directorate
MTSO	Management and Technical Support Office
NASA	National Aeronautics and Space Administration
NESC	NASA Engineering and Safety Center
NRB	NESC Review Board
PFO	Patent Foramen Ovale
PRP	Prebreathe Reduction Program
RPE	Rate of Perceived Exertion
S&MA	Safety and Mission Assurance
SEO	Systems Engineering Office
SLSD	Space and Life Sciences Directorate
SSP	Space Shuttle Program
VGE	Venous Gas Emboli

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14. ABSTRACT The performance of extravehicular activity (EVA) by National Aeronautics and Space Administration astronauts involves the risk of decompression sickness. This risk has been mitigated by the use of oxygen "prebreathe" to effectively wash out tissue nitrogen prior to each EVA. Now that the Space Shuttle Program (SSP) is being retired, high-pressure oxygen will become a limited resource. The In-Suit Light Exercise (ISLE) Prebreathe Protocol offers several potential benefits including its potential to save 6 pounds of oxygen per EVA. At the request of the NASA Engineering and Safety Center, the peer review convened on October 14, 2010. The major recommendation of the Review Committee was that the ISLE protocol was acceptable for operational use as a prebreathe option prior to EVA. The results from the peer review are contained in this document.					
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