Announcement of Opportunity soliciting for proposals using the Human Spaceflight Analogue “Bedrest”

AO-16-BR

Images : DLR.

Letter of Intent due:

February 15th, 2016

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Proposal due:

March 15th, 2016

Summary for the Bedrest Study Research Opportunity

- The Directorate of Human Spaceflight and Robotic Exploration Programmes of the European Space Agency announces an opportunity to propose human research using the human spaceflight analogue "bedrest". Proposals selected in response to this Announcement of Opportunity (AO) will be conducted in the bedrest facility of :envihab located in Cologne, Germany at the German Aerospace Center Institute and will make use of the :envihab short-arm human centrifuge to create Artificial Gravity as a countermeasure. Subjects will undergo 60 days of 6° head-down tilt bed rest. They will be ambulatory for two weeks prior to and after bed rest.

- The planned bedrest study will be implemented jointly with NASA who have released a dedicated NASA Research AO in late 2015. International cooperation to strengthen scientific excellence in this bedrest study is strongly encouraged. European investigators who have already responded to the NASA Research AO with proposals as principal investigators or co-investigators shall not submit duplicate proposals to this ESA AO to avoid duplications during the peer review.

- Eligibility: The scientific institution for which the coordinator of a proposal is working must be located in one of the ESA member or associated member states that contribute to the ELIPS Period 4: **Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Ireland, Italy, The Netherlands, Norway, Romania, Sweden, Switzerland, United Kingdom**. Scientists from ESA Member States that do not contribute to the ELIPS Programme and scientists from other European countries having a cooperation agreement with ESA, are encouraged to enquire with their national space organisation about the conditions for their participation in submitting proposals to ESA.

- Submission of proposals will be done electronically via NASA's NSPIRES website (http://nspires.nasaprs.com/).

- For questions related to this Announcement of Opportunity please contact:
  Dr. med., Dr. rer. nat. Thu Jennifer Ngo-Anh
  AO-specific email: bedrest@esa.int

- Important dates:
  - Letter of Intent due: 15th of February 2016
  - Proposal workshop (at ESA/ESTEC, NL): 22nd of February 2016
  - Proposals due: 15th of March 2016

- Implementation schedule: Preparation of the study will start in the second half of 2016. Start of the study is foreseen in 2017.

Table of Content

1 Introduction

Head-down tilt bedrest is a well-established terrestrial model for some of the physiological changes occurring during spaceflight. Studies performed before, during and after bedrest allow both fundamental research, e.g. on mechanisms of the observed changes, and the evaluation of new countermeasure concepts for long-duration space exploration missions. ESA has been organising bedrest studies regularly since many years and is with this Announcement of Opportunity soliciting proposals for a 60 day-bedrest study to be conducted jointly with NASA using the bedrest facility of :envihab located in Cologne, Germany at the German Aerospace Center Institute.

2 Artificial Gravity as a countermeasure

Artificial gravity (AG) generated by centrifugation has the potential to mitigate physiological deconditioning caused by prolonged exposure to weightlessness. Because all physiological systems are challenged through the application of AG, it has been considered that AG has the unique feature of being a multi-system countermeasure for mitigating the effects of weightlessness. While it is obvious that AG cannot address all of the problems associated with long-duration spaceflight, such as the challenges of radiation exposure, altered day-night cycles, and the psychological issues that are likely to arise from extended confinement and isolation, there is scientific consensus that AG offers the potential to address the debilitating and potentially fatal problems of bone loss, cardiovascular deconditioning, muscle weakening, sensorimotor and neurovestibular disturbances, and regulatory disorders. In contrast to traditional countermeasures, AG can be considered as an integrated countermeasure because it addresses all of these systems at once. Therefore the use of AG might be the best solution for human health protection during human long-duration deep space missions.

Previous investigations have studied the effects of intermittent AG using a short-radius centrifuge in human subjects deconditioned by 6º head-down tilt bed rest (HDBR) ranging from 4 to 21 days (Nyberg et al. 1966; Yajima et al. 1994; Lee et al. 1997; Iwasaki et al. 1998; Katayama et al. 2004; Iwase 2005; Young & Paloski 2007; Linnarsson et al. 2015). Results showed that daily exposure to 1-2 Gz at the heart for 0.5-2 hours was effective in mitigating orthostatic intolerance and maintaining exercise capacity after HDBR. Of particular interest is a recent study that compared daily AG sessions generating +1 Gz at the heart for 30 minutes continuously (1 x 30 min) to 6 bouts of 5 minutes (6 x 5 min) separated by 5 minutes of rest (Linnarsson et al. 2015). The 6 x 5 min +Gz intervention was found to be the most effective in preserving orthostatic tolerance after HDBR, and appeared equivalent to a continuous 60-min exposure to +Gz stimulation in other studies. It was also better tolerated by the subjects.

Unfortunately, these bedrest studies were too short to evaluate the effectiveness of intermittent AG on bone and muscle structure and strength, and on sensorimotor deconditioning. Also, functional and cognitive performances, which are essential for the success of exploration-type space missions, were not tested during these studies.
Therefore, ESA is initiating an AG research programme to 1) identify the specific gaps associated with AG as a potential countermeasure, 2) perform analyses between AG and the currently used and tested non-AG countermeasures, and 3) initiate international collaboration for the most efficient and strategic use of available resources.

3 The bedrest study targeted with this AO

This AO is soliciting proposals to be implemented in a 60-day bedrest study in 6° head-down tilted subjects. Selected proposals will be implemented in the :envihab bedrest facility in Cologne, Germany and will make use of the :envihab short-arm human centrifuge. Subjects will be ambulatory for two weeks prior to and after bedrest. This time will allow for standardized measures data collections (see Annex 1) and recovery after bedrest. During the bedrest phase, subjects will be randomly assigned to one of 3 experimental groups (n=8 in each group; total n=24).

Experimental groups:

- Group 1: 6° head-down tilted bedrest with no centrifugation (control).
- Group 2: 6° head-down tilted bedrest with supine centrifugation at +1Gz at the heart for 30 minutes per day.
- Group 3: 6° head-down tilted bedrest with supine centrifugation at +1Gz at the heart for 6 bouts of 5 minutes per day (sessions 2-6 are separated by 5 minutes of rest).

Depending on the height of the subjects and their position relative to the rotation axis of the centrifuge, the rotation rate will range from 25 to 30 rpm. This rate corresponds to about +2Gz at the feet. Angular acceleration and deceleration during spin-up and spin-down of the centrifuge will not exceed $5°s^{-2}$. For more information on the :envihab short arm centrifuge capabilities see the :envihab Short Arm Centrifuge document posted along side of this solicitation.

The primary objective of this Announcement of Opportunity is to compare the protective effects of one single daily bout versus multiple daily bouts of AG on physiological functions that are affected by weightlessness. A secondary objective is to document the user's point of view, such as subjective rating of comfort/discomfort, perceived exhaustion, perceived benefits, and any other psychological issues associated with the applied AG- protocols. **Please note that proposals of new or adapted countermeasures are not part of this AO.**

Proposals should address physiological areas, which could be affected by bedrest and the countermeasure used. Any type of research field can be addressed.

4 Proposal Evaluation and Selection Procedures

An independent scientific merit (peer) review coordinated by the NASA Peer Review Service will be performed using the following criteria:

Significance:
Does this study address a research emphasis stated in this solicitation? Does the study test a significant hypothesis or produce data that would enable a significant hypothesis to be generated? If the study is non-hypothesis driven, are the data produced needed to understand or reduce the risk addressed by the research emphasis? If the task will produce a software model or tool, how will it serve to better quantify or mitigate a risk? If the aims of the application are achieved, how well will the product(s) address the research emphases? If the aims of the application are achieved, how will scientific knowledge or technology advance?

Approach:
Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Is the proposed approach likely to yield the desired results? Does the applicant acknowledge potential problem areas and consider alternative tactics? If applicable, has the applicant included a range of reasonable sample sizes for a proposed study with proper justification?

Statistical Plan:
A thorough statistical section must be included which includes a power analysis for the estimate of sample size and the comparison of males and females unless compelling evidence is provided that shows that no sex differences are expected. Does the study provide adequate justification for sample size? For example, is the choice of primary outcome relevant for the stated Aims? Are assumed effect magnitudes reasonable? Are assumed variability estimates reasonable? Are they estimated properly? Are they relevant for the proposed experimental design and data analysis methodology? What Type I and Type II errors are assumed? Is there room for a tradeoff here to accommodate sample size constraints and still provide useful information from the study? Do the investigators provide a reasonable data analysis plan? For example, is it appropriate for the proposed experimental design (e.g. repeated measures)? Does it address research hypotheses or aims? Is it robust to the sampling and other constraints associated with the research venue?

Risk Mitigation:
For a study quantifying risks to crew health or performance, does the study adequately improve the understanding of the adverse consequences, the probability of its occurrence, or the timeframe in which the risk must be addressed? For a study developing technology, will the research product reduce the risk to crew health or performance, reduce its impact or better define it and is the technology feasible within the confines of the operational environment?

Investigators:
Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and any co-investigators? Is the evidence of the investigators' productivity satisfactory?

Environment:
Does the scientific environment in which the work will be performed contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In the review, each proposal will receive a scientific merit score between 0 and 100 points. As a result of the scoring the proposals will receive one of the following marks:

SCORE DESCRIPTION	SCORING RANGE
EXCELLENT: Scientific/technical merit of the proposal places it among the top 10%. A proposal that has several strengths, no major weaknesses, and very few or no minor weaknesses.	90 - 100
VERY GOOD: Scientific/technical merit of the proposal places it among the top 20% (but NOT the top 10%). A proposal that has one or more strengths, no major weaknesses, and minor weaknesses that are substantially outweighed by the strengths.	80 - 89
GOOD: Scientific/technical merit of the proposal places it among the top 30% (but NOT the top 20%). A proposal that has no major weaknesses, several minor weaknesses, but sufficient strengths to balance and compensate for the minor weaknesses.	70 - 79
FAIR: Scientific/technical merit of the proposal places it among the top 50% (but NOT the top 30%). A proposal that has one or more major weaknesses, and in which the major and minor weaknesses clearly compromise any strengths.	50 - 69
POOR: Scientific/technical merit of the proposal places it in the lower 50%. A proposal that has several major weaknesses that would require major revisions to correct.	<50
NRFC: Not recommended for further consideration. A proposal that is judged by unanimous consent of the panel to be unlikely to benefit from revision *or* a revised proposal in which little or no effort has been made to address previous review comments.	NRFC

Only those proposals that are most highly rated in the merit and relevance review process will undergo additional reviews for feasibility. A panel of technical experts from ESA and NASA will evaluate the feasibility of carrying out the experiment and the potential for establishing teams of investigators to optimize utilization of human subjects, samples, data, and resources. This review will be conducted by technical experts familiar with the development and conduct of bedrest studies.

The outcome of all these evaluation steps, with support by ESA's advisory bodies, will be used in the development of ESA's selection recommendation to its relevant Programme Board (PB-HME). The current aim is to propose the experiment selection to the PB-HME meeting in the September 2016 timeframe.

Thereafter, an integrated protocol with the standardized measurements (for a list of measures please see Annex 1) and the protocols from the selected experiments will

have to be developed before being submitted to the institutional review board for final acceptance. This process is typically done in Investigator Working Group meetings and will start in the second half of 2016.

5 Data Rights

5.1 General

The general data policies of ESA's Directorate for Human Spaceflight and Robotic Exploration Programmes will apply to all data resulting from the experiments in the context of this AO. The main relevant aspects, in their specific implementation for bedrest activities, are described in this and the following paragraphs.
Final results of the study shall be made available by the scientific teams to the scientific community through publication in appropriate journals or other established channels as soon as practicable and consistent with good scientific practice. In the event such reports or publications are copyrighted, ESA shall have a royalty-free right under the copyright to reproduce, distribute, and use such copyrighted work for their purposes.

5.2 Practical implementation of data policies

Three types of experiment data are identified:

Category 1: data will be obtained and processed under the responsibility of the Principal Investigator (PI) for the experiment protocol. Data not requested by any other PI may be used exclusively by the PI for scientific purposes. For data requested by more than one PI, each PI must agree before the study starts as to the conditions for the data usage for scientific purposes. This category of data shall be referred to as "PI proprietary data." The PI proprietary data may be used by the sponsoring agencies for internal purposes. The sponsoring agencies agree that this data will not be made public for 1 year after the completion of the study's clinical phase (last point of data collection in the ambulatory recovery period following the bed rest).

Category 2: data comprise "International Standard Measures" (a list of measures to be collected can be found in Annex 1), as defined and owned by ESA, NASA and other participating agencies. PIs can apply, and are even encouraged to use the standard measures. ESA and NASA, in consultation with the bedrest steering committee, will decide on the first publication rights for the standard measures.
Scientific merit of the respective proposal and thematic relevance will be the key factors influencing the ranking.

There will also be common clinical data (**Category 3**) for usage by all PIs and science team members. This will be distributed to PIs.

In case follow-up points long after the bedrest per se are required for a project, a PI can apply for extension of the one-year exclusive publication period by submitting a scientific report in the format of a manuscript 1 year after the completion of the study's clinical phase.

5.3 Data Access

A PI can access proprietary data from other PIs participating in the study through a written data sharing agreement (signed by the involved PIs). ESA will ensure that a data-sharing plan among the participating PIs is established prior to the beginning of the bedrest study.
All PI proprietary data and standard measures will be treated as medical confidential information by the participants and ESA.

5.4 The Erasmus Experiment Archive (EEA)

The EEA is an ESA service to the international scientific community. Abstracts, from all European microgravity experiments performed to date are collected in this database. Experimenters sponsored by ESA have the obligation to provide these abstracts themselves. Special emphasis is placed on the completeness of the list of references of articles where the experiment results can be found.
The database includes a full-text search capability to retrieve information on experiments in a certain discipline, subject, mission, or by investigator name. The EEA covers both physical and life sciences, and can be found at the following URL: http://eea.spaceflight.esa.int
This database includes also a large number of pictures, as well as video sequences documenting experiment abstracts.
Scientists in Europe who have performed experiments, be it in orbiting or ground-based facilities are urged to either provide an abstract on each of their experiments, or to provide information enabling the updating of their existing abstracts, in particular the list of articles published. Please e-mail your new abstracts or the updated information for already existing abstracts to the EEA Curator.

5.5 Acknowledgement

Any publication on the results generated during bedrest studies solicited in this AO must acknowledge ESA's sponsorship of the study.

5.6 Support of Education and Outreach

The activities covered in this AO provide an opportunity for ESA to enhance and broaden the public's understanding and appreciation of research facilitated by ESA's Human Spaceflight and Robotic Exploration Programmes Directorate.
Therefore the investigators of selected experiments are expected to promote and communicate their experiments to a wide audience (general public, colleagues, involvement of students) and to support ESA in the event of organised press conferences, educational events, publications etc.

6 Proposal Preparation Guide

6.1 Contact

For questions related to this Announcement of Opportunity please contact

Dr. med., Dr. rer. nat. Thu Jennifer Ngo-Anh
AO-specific email address: bedrest@esa.int

It is planned to organise a proposal workshop in connection to this research announcement on February 22nd, 2016. The workshop will take place at ESTEC, Keplerlaan 1, Noordwijk, The Netherlands. This will be an opportunity to clarify potential questions or gather contacts for cooperative research projects.

Please indicate your interest in participating in this workshop to the above-mentioned contact email, for planning, registration and logistical information and distribution purposes, at the latest by 15th of February 2016 together with a Letter of Intent.

6.2 Time Schedule

Letter of Intent due:	15th of February 2016
Proposal workshop	22nd of February 2016
Proposals due:	15th of March 2016

6.3 Letters of Intent

To facilitate timely proposal processing (e.g. organisation of peer review), potential investigators are requested to confirm their plans to submit a proposal in response to this announcement via a Letter of Intent (LoI). The LoI is not binding.
LoIs will be distributed to the participants of the proposal workshop to facilitate possible cooperations. This should be taken into account when formulating the LoI, e.g. by avoiding inclusion of unpublished data.
The LoI is requested by **15th of February 2016**. LoIs should be prepared using the template found on the AO website. LoIs should be submitted as PDF file to the email address: **bedrest@esa.int**

6.4 Funding

Costs related to access to the bedrest facility and subjects are covered by ESA. However, ESA cannot financially support the work of selected experimenters. Any additional expenses related to the proposed work of an experimenter, including costs for travel (e.g. to meetings) and subsistence are considered investigator-related costs,

which are not sponsored by ESA. Funding from national agencies / organisations, universities, or other institutions is required to cover investigator-related costs.
Due to the experience in recent years, ESA strongly advises all scientists to contact their national representatives (see ANNEX 2) to investigate possible national funding procedures and timelines as well as probability of funding in order to identify alternative funding sources if necessary. As a minimum, it is recommended to submit the proposal to their national bodies in parallel with their application in response to this AO, in order to commence applying for national funding as early as possible.
If the proposed experiment is selected, a proof of appropriate funding is mandatory before commencing implementation of the proposals.

6.5 Proposal Submission

For this research announcement proposals must be submitted online through the NASA NSPIRES web site (http://nspires.nasaprs.com/) by

15th of March 2016

The online submission process includes several steps, during which proposers will be asked to fill in the proposal title, acronym, abstract and science team contact details (proposers will be asked to fill in online the names and full contact details of the Principal Investigator and all Science Team Members (STMs), specifying the members' institutional affiliations). A signature version of this form will not be requested.
The information submitted will then be compiled by the system. Proposers will then be required to upload their proposal, established following participating agencies' guidelines, as a single PDF document. The compiled information and the uploaded proposal will then be automatically merged and forwarded to proposers. This document, stored in the NSPIRES database, will represent the reference document for future queries.

Non-US proposers must register in NSPIRES using the NSPIRES International Office as their affiliate. Below are the instructions on how to complete this.

Step 1: ONLY if you do not already have an NSPIRES account:
1) To register, go to http://nspires.nasaprs.com and click on the "Registration Information" link in the Member Login Box on the right side of the page
2) Click on the yellow "Begin Registration" button on the Registration Information page and complete the requested information to obtain an account
3) Activate your account by responding to the instructions provided in an automatic email sent by the NSPIRES system

Step 2: Linking with the NSPIRES International Office organization (Affiliation).
It is your responsibility to request this affiliation at least two weeks in advance of the proposal due date in order to guarantee an approved affiliation for proposal submission.
1) International proposer logs into NSPIRES (http://nspires.nasaprs.com)

2) Select the “Account Management” link on the NSPIRES Welcome page
3) Select “Affiliations” on the Account Management page
4) Click on the “Add Affiliations” on the Current Affiliations page
5) Type in “NSPIRES International Office” and click “Search”
6) Select the radio button for “NSPIRES International Office” under the search results and click the “Select” button
7) Verify that you have selected NSPIRES International Office and click “Continue”
8) Complete the Affiliation Address Book Data.
9) Click “Continue”
10) Click “OK” on the Affiliations page
11) Return to the Affiliations page in the Account Management section of NSPIRES to confirm that your affiliation request has been approved.

To create a Proposal:

1. Log in to NSPIRES
2. Select the “Proposals/NOIs” link
3. Select the “Create Proposal” link
4. Select “Solicitation” as your source and then choose solicitation “Announcement of Opportunity soliciting for proposals using the Human Spaceflight Analogue “Bedrest” (non-US proposers only).”

Please refer to the NSPIRES tutorial at http://nspires.nasaprs.com/tutorials/index.html for on-line help. All information entered will remain private until the electronic submission is completed.

All proposals must be contained in one single and non-protected PDF document, and include the following material, in this order:
1) Project Description (see below)
2) Management Approach (see below)
3) Biographical Sketches (see see below)
4) Special Matters: specific information on human subjects protocol approval required
5) Appendices, if any; reviewers are not required to consider information presented in appendices

The NSPIRES system may by default ask you to provide responses to business data questions pertaining to international collaboration, environmental impact, and US Civil Servant applicants. Please answer “no” to any business data question posed with a yes/no response. These questions only pertain to US investigators.

The NSPIRES Help Desk is available Monday through Friday, 8AM - 6PM Eastern Time to assist in answering questions related to the NSPIRES system. The NSPIRES Help Desk cannot assist with proposal content or science questions. The NSPIRES Help Desk can be reached at nspires-help@nasaprs.com or +1-202-479-9376.

Project Description

The length of the Project Description section of the proposal shall not exceed twenty (20) pages using regular (12 point) font. The proposal should contain sufficient detail

to enable a reviewer to make informed judgments about the overall merit of the proposed research and the probability that the investigators will be able to accomplish their stated objectives. The proposal should clearly indicate the relationship between the proposed work and the research emphases defined in the solicitation. The development of a clear hypothesis, along with the available data evidence, should be emphasized in this section. In addition, the proposal should provide evidence of completed or planned ground research to justify the experiment. In particular PIs should refer to agency-specific solicitations for instructions regarding additional information that should be included in the proposal.

Management Approach

Each proposal must specify a single PI who is responsible for carrying out the proposed project and coordinating the work of other personnel involved in the project. In proposals that designate several senior professionals as key participants in the research project, the management approach section should define the roles and responsibilities of each participant and note the proportion of each individual's time to be devoted to the proposed research activity. The proposal must clearly and unambiguously state whether these key personnel have reviewed the proposal and endorsed their participation.

Personnel/Biographical Sketches

The PI is responsible for direct supervision of the work and must participate in the conduct of the research regardless of whether or not compensation is received under the award. A short biographical sketch of the PI, including his or her current position title, educational background, a list of major publications, and a description of any exceptional qualifications, must be included. In chronological order (concluding with present position), list previous employment, experience, and honors. Include present membership on any government public advisory committees. List in chronological order the titles, authors, and complete references to all publications pertinent to this application. If the list of publications exceeds two pages, select the most pertinent and recent publications. Do not exceed two pages. Omit personal information that does not merit consideration in evaluation of the proposal. Complete this part of the application for other senior professional personnel who will be directly associated with the project. Provide the names and titles of any other scientists and technical personnel associated substantially with the project in an advisory capacity. Universities should list the approximate number of students or other assistants, together with information as to their level of academic attainment. Any special industry-university cooperative arrangements should be described.

Special Matters

The Special Matters section must contain appropriate statements regarding human subject provisions and/or the use of vertebrate animals (not applicable in this case).

Letters of Collaboration/Support

Include letters of support from collaborators.

Appendices

Appendices may be included, but investigators should be aware that reviewers are not required to consider information presented in appendices.

Experiment Data Sheet

Please fill the details of your experimental protocol in the Experiment Data Sheet form that is part of the Proposal template.

Annex 1: International Standard Measures

An overview of the standard measures to be performed during all flight analog/bed rest studies is presented here. Standard measures provide a characterization of the physiologic responses to bed rest in humans across disciplines. These protocols are integrated with science investigation requirements on a non-interfering basis. The standard measures can be utilized to provide a basis for comparison of bed rest results with results from spaceflight investigations, and provide ancillary data to individual investigators. A schedule of the standard measures is located after the descriptions.
Descriptions of the standard measures are described below for each discipline and include methodology for each standard measure. When applicable, equipment manufacturers are listed for each test. These manufacturers are provided as examples of the type of equipment that may be used to complete a particular test. A summary of the standard measures and schedule for testing is listed in the Table A-2 below. The testing schedule is subject to change depending upon investigator requirements.

Table A-2. Schedule of Required Standard Measures

Standard Measure	Pre-Bed Rest	Head-Down Tilt Bed Rest	Post Bed Rest
Postural Equilibrium Control	BR-1		BR+0
Treadmill Locomotion Test	BR-2		BR+0
Tilt test (with echo)	BR-5		BR+0
Maximal Aerobic Capacity	BR-4		BR+0
Muscle strength	BR-5		BR+2
Vertical Jump	BR-5		BR+0
Bone mineral density	BR-13		BR+13
Bone markers	BR-3		BR+0
Nutrition/Hematology	BR-3		BR+0
Immunology	BR-3		BR+0
Optical Coherence Tomography	BR-3		BR+0
Intraocular Pressure	BR-3		BR+0
Ocular Ultrasound	BR-3		BR+0
Positive and Negative Affect Scale	BR-13, BR-1	BR14, BR28, BR42, BR56	BR+1, BR+13
General Health Questionnaire	BR-13, BR-1	BR14, BR28, BR42, BR56	BR+1, BR+13

Note. Data collection time points designated as BR- are pre-bed rest, those designated as BR are during bed rest, and those designated as BR+ are post bed rest. Time points for data collection are examples and may change depending upon requirements of investigator studies.

Sensorimotor Standard Measures

Postural Equilibrium Control

This test will characterize changes in postural control following bed rest. This test utilizes computerized dynamic posturography (CDP) to quantitatively assess both sensory and motor components of postural control. The Sensory Organization Tests (SOTs) objectively evaluate one's ability to make effective use of (or suppress inappropriate) visual, vestibular, and proprioceptive information for balance control.

The Motor Control Tests (MCTs) evaluate one's ability to automatically recover from unexpected support surface perturbations.
Postural stability will be evaluated using a computerized dynamic posturography system (Equitest, NeuroCom International, Clackamas, OR). The SOT objectively assesses one's ability to make effective use of (or suppress inappropriate) visual, vestibular, and proprioceptive information for balance control. The more challenging SOT conditions involve disrupting proprioceptive and visual feedback by rotating the support surface and visual surround in proportion to body sway, referred to as sway-referencing. The standard SOT protocol with head erect is comprised of six conditions involving two support surface conditions (fixed and sway-referenced) and three visual conditions (eyes open, eyes closed and sway-referenced surround). Two modified SOT conditions continue to be used to increase sensitivity and specificity by including dynamic head tilts with eyes closed on either fixed (2M) or sway-referenced support surface (5M). The dynamic tilts involve pitching the head at 0.33 Hz (± 20°) paced by an audible tone. For each SOT trial, data are recorded for 20 seconds or until there is a fall. Table A-3 describes the SOT tests.

Table A-3. SOT Tests

Condition	Support Surface	Vision	Head
1	Fixed support	Eyes open, fixed surround	Erect
2	Fixed support	Eyes closed	Erect
3	Fixed support	Sway-referenced surround	Erect
4	Sway-referenced	Eyes open, fixed surround	Erect
5	Sway-referenced	Eyes closed	Erect
2M	Fixed support	Eyes closed	Dynamic (0.33 Hz, ± 20°)
5M	Sway-referenced	Eyes closed	Dynamic (0.33 Hz, ± 20°)

Note. SOTs 5 and 5M are required posturography tests. SOTs 1 to 4 and 2M are recommended.

The MCTs assess the patient's ability to quickly and automatically recover from unexpected support surface perturbations. Large forward and backward platform translations (400 ms, amplitude scaled to the subject height, approximately 2.3 inches for a 6-foot-tall subject) are performed to elicit automatic postural responses. Throughout each SOT and MCT trial, subjects are instructed to maintain stable upright posture with arms folded across the chest. External auditory orientation cues are masked by white noise supplied through headphones. Center-of-mass sway angles are estimated from instantaneous anterior-posterior (AP) and medial-lateral (ML) center-of-force positions computed from force transducers mounted within the EquiTest force plates. The AP peak-to-peak sway angle (p-p sway) is used to compute the equilibrium score (EQ), where 12.5 is the maximum theoretical p-p sway.

Treadmill Test

The level of conditioning and consequently, the effectiveness of the training performed by crewmembers are also determined in long-duration flight according to the parameters of the treadmill test with gradually increasing locomotor loads on the treadmill. A distinctive feature of the test is the standardization of the sequence and length of each of the five load levels with voluntary selection of work intensity within each level. The speed limits of slow, moderate, and fast running are self-selected by

the subject. Parameters collected during each of the five load levels are running speed (m/s) and heart rate (bpm). The intensity of work performed is then expressed as the ratio of peak heart rate to peak running velocity (beats/60 m).
The treadmill test consists of several steps: warm-up walking for 3 minutes, slow running for 2 minutes, moderate running for 2 minutes, fast running for 1 minute, and walking for 3 minutes as the final step. The test is performed in idling regimen (passive mode) of treadmill. In this mode, the treadmill belt is driven by the force of the running subject. The length of the test is 11 minutes, and the energy expended during the experiment is approximately 100 kcal. Steps for this test are summarized in Table A-4.

Table A-4. Steps for Locomotor Test

Steps	Time (min)
Warm-up walking	3
Slow running	2
Moderate running	2
Fast running	1
Walking	3

Cardiovascular Standard Measures

Tilt Test

The tilt test is used to assess orthostatic tolerance before and after bed rest. Subjects are instrumented while supine and this position is maintained while baseline data are collected for 5 minutes. The table is then tilted to 80° placing subjects in a head-up tilt position at a rate of approximately 7°/s. Subjects remain in this position for 15 minutes or until they exhibit symptoms of presyncope. Total time standing at 80° head-up tilt is recorded.
During the test, continuous measures are obtained for blood pressure, electrocardiography (ECG), and Doppler ultrasound of blood flow velocity at the suprasternal notch. Finger arterial blood pressure is sampled at 200Hz using a photoplethysmography device (Finometer Pro, Finapres Medical Systems, Netherlands). This device uses a hydrostatic adjustment routine to provide an accurate estimation of blood pressure independent of sensor location with respect to the heart. Oscillometric brachial artery pressure is also measured using a cuff placed around the upper arm every minute (Dinamap XL Vital Signs Monitor, GE Medical Systems Information Technologies, Milwaukee, WI). Systolic and diastolic blood pressure are recorded and mean arterial pressure (MAP) is calculated as MAP = [(2 × diastolic)+systolic] / 3. ECG data are collected at 100Hz using a 5-lead system (Escort II, Medical Data Electronics, Arleta, CA). Heart rate measures are derived from the ECG and ECG collection is synchronized with the suprasternal notch Doppler ultrasound signals for stroke volume and cardiac output calculations. Two-dimensional echocardiography is used to obtain the aortic annulus diameter from the parasternal long axis during supine rest prior to data collection. The aortic blood velocity time integral is measured for each beat during supine rest and during the period of 80° head-up tilt. These Doppler measurements are made at the suprasternal notch using a 1.9 MHz pulsed wave Doppler probe (Biosound MyLab Gold,

Indianapolis, IN). Images are stored digitally for subsequent analyses. To insure accuracy, images from at least three cardiac cycles during inspiration are independently analyzed by two experienced sonographers. Stroke volume (annulus diameter x velocity time integral) and cardiac output (stroke volume × heart rate) are calculated.

Maximal Aerobic Capacity (VO2max)

Maximum aerobic capacity is assessed using a graded exercise protocol on an electronically-braked cycle ergometer (Lode Excalibur Sport; Lode B.V., Groningen, The Netherlands), and a metabolic cart for gas exchange determination (TrueOne® 2400, ParvoMedics, Sandy, UT). For accurate collection of gases, subjects wear a nose clip and breathe through a respiratory valve. The graded exercise protocol provides an individualized approach to achieve subjects' maximum aerobic capacity using small increments in workload. Subjects warm up cycling at a light workload (0 to 75 Watts) for 1 to 3 minutes. During testing, subjects maintain a pedaling cadence of 70 to 75 revolutions per minute (rpm). Workload begins at 50 Watts for 3 minutes and is then increased by 25 W every minute. Increasing workload in small increments with each minute of exercise allows for evaluation of ventilatory threshold and VO2max. Using this protocol, maximal exercise is achieved in approximately 8 to 15 minutes.

Heart rate is monitored continuously during testing (Q-Stress ECG monitor, Quinton Instruments, Seattle, WA). Blood pressure is measured during each of the first 3 stages, and every 2 minutes during the subsequent 1-minute stages, using a sphygmomanometer and stethoscope. Measures collected (or derived) through gas exchange data include VO2, carbon dioxide elimination (VCO2), RER, minute ventilation (VE), anaerobic threshold and ventilatory threshold. Workload is also recorded.

MUSCLE STANDARD MEASURES

Muscle Strength

Isometric and isokinetic testing provide assessments of muscle strength and endurance. These assessments can be completed using an isokinetic dynamometer such as the Biodex Dynamometer (Biodex Medical Systems, Inc., Shirley, NY).

Isometric maximum voluntary contractions will be completed for muscles of the knee and ankle. This test provides a very fast and reliable measurement of isometric strength of two important lower body muscle groups.

To test isometric knee strength, the seated subject is positioned in the dynamometer with the knee flexed at 60°. The subject then performs three sets of maximum contractions alternating between flexion and extension muscle contractions. Each muscle contraction should last 5 to 7 seconds with 30 seconds of rest between flexion/extension contractions.

For testing isometric ankle strength, the subject is placed in the prone position with the ankle positioned at 90°. Three sets of maximum contractions are performed alternating between plantar flexion and dorsiflexion muscle contractions. Muscle contractions should last 5 to 7 seconds with 30 seconds of rest between plantar and dorsiflexion contractions.

For all isometric muscle testing, the highest value of torque (Nm) obtained is considered the subject's maximum. If a subject continues to improve at the third contraction, proceed with testing until no further improvement is observed.

Isokinetic muscle testing is used to assess strength of knee, ankle and trunk musculature. In addition, endurance testing for muscles of the knee is also performed. As a warm-up, subjects complete 5 minutes of light exercise (50 Watts) on a cycle ergometer. For each isokinetic test, muscles are warmed up prior to testing by completing 5 contractions with increasing force levels. A 2 to 3 minute rest period is provided between testing of each muscle group. For standardization purposes, knee and ankle testing are performed on the right lower extremity.
For isokinetic testing of the knee, the subject is placed in a seated position. Knee range of motion on the dynamometer is set for 20° to 95°. The weight of the limb is assessed with the knee positioned at 30°. Isokinetic peak torque (Nm) is assessed at a speed of 60°/s. The subject performs 3 repetitions of continuous concentric extension and flexion motion at maximal effort.
Subjects are provided a 2-minute rest period prior to endurance testing. Endurance testing of the knee is assessed at a speed of 180°/s. The subject performs 20 repetitions of continuous flexion and extension motion at maximal effort. Total work in Nm is recorded. Table A-5 summarizes the isokinetic protocol for the knee.

Table A-5. Isokinetic Knee Protocol

Speed	Warm-up	Test Repetitions	Rest
		Knee (Concentric)	
0°/s (Isometric Mode)	None	Practice Test (2 Sub, 1 Near Max)	60 seconds
0°/s (Isometric Mode)	None	3 Max	60 seconds
60°/s	2 Submax	3 Max	60 seconds
		Knee (Endurance)	
180°/s	2 Submax	20 Max	Set-up for next test

Isokinetic testing of the ankle is done with the subject in the prone position. Range of motion of the dynamometer is adjusted to 5° less than the subject's maximum position of dorsiflexion and 5° less than the subject's maximum position of plantar flexion. Weight of the limb is assessed with the ankle positioned at 15°. Isokinetic peak torque (Nm) is assessed at a speed of 30°/s. Three repetitions of continuous concentric dorsi- and plantar flexion contractions are performed at maximal effort. A rest period of about 2 minutes is provided before testing is repeated to assess peak torque (Nm) for eccentric muscle contractions. Table A-6 summarizes the isokinetic protocol for the ankle.

Table A-6. Isokinetic Ankle Protocol

Speed	Warm-up	Test Repetitions	Rest
		Ankle (Concentric)	
30°/s	2 Submax	3 Max	60 seconds
		Ankle (Eccentric)	
30°/s (Passive Mode)	None	Practice Test (3 Submax)	60 seconds
30°/s (Passive Mode)	None	3 Max	60 seconds
30°/s (Passive Mode)	None	Practice Test (3 Submax)	60 seconds
30°/s (Passive Mode)	None	3 Max	During set-up for next test

Assessment of isokinetic trunk strength is done with the subject in a standing position. Range of motion on the dynamometer is set for 0° to 90° of motion. Weighing of the trunk is not required. Peak torque (Nm) is assessed at a speed of 60°/s. The subject performs 3 repetitions of continuous concentric flexion and extension motion at maximal effort. Table A-7 summarizes the isokinetic protocol for the trunk.

Table A-7. Isokinetic Trunk Protocol

Speed	Warm-up	Test Repetitions	Rest
		Trunk (Semi-standing position)	
60°/s	2 Submax	3 Max	Test Complete

Vertical jump is used as an assessment of whole-body-power output. A ground-reaction platform (Kistler Instrument Corp., Amherst, NY) is used for data collection. Data are collected with a custom LabVIEW software program (National Instruments Corp., Austin TX) and sampled at 1000 Hz using a National Instruments data acquisition system (National Instruments Corp., Austin TX). Prior to the jumping task the subject performs a warm-up session and is instructed to perform 3 warm-up squats. The subject is then instructed to perform 2 to 3 practice countermovement jumps at 50% of maximum effort to ensure that proper technique is understood. Countermovement jump begins by anchoring the hands on the waist while standing with erect posture. The movement is performed by the subject quickly dropping into a squat then reversing the direction by pressing into the platform with maximum force with the aim to jump as high as possible. This motion does not allow pause during the movement and requires the hands to be anchored to the hips at all times to remove moments of inertia contributed by the arms swinging. Once the subject warms up and proper technique is demonstrated, the operator allows the subject to attempt 3 maximum effort jumps. Prior to jumping, body mass is measured during quiet stance assuming acceleration due to Earth's gravity to be 9.8 m/s2, then the subject is instructed to jump and encouraged to elevate the head as high as possible. The subject rests 60 to 90 seconds in between each jump or longer if the subject desires more time between tests. The sum of the vertical ground reaction forces collected from the force plate are divided by body mass to determine the subject's acceleration profile. To calculate the subject's jump height a double integration of the acceleration profile is computed. Instantaneous power is calculated as the product of acceleration and velocity. Variables of peak acceleration in m/s2 (Apeak), peak velocity in m/s (Vpeak), jump height in cm (Hpeak), and peak power in kW (Ppeak) are then assessed as the maximum of these respective curves.

BONE STANDARD MEASURES

Bone Mineral Density

Measures of 2-dimensional bone mineral density (BMD) are obtained by dual-energy X-ray absorptiometry (DXA) using, e.g., a Hologic Discovery Unit whole body densitometer (Hologic, Inc., Bedford, MA). Scans are obtained in triplicate from the following sites: whole body, lumbar spine, and hip. The forearm and calcaneus are recommended sites depending upon study specific requirements. Triplicate values for each scan type are averaged to improve measurement precision. Variables of BMD

and bone mineral content (BMC) are derived from the scans and percent change from pre- to post bed rest is calculated at each site.

Bone Markers

Bone turnover markers are used to examine overall bone metabolic changes during bed rest. Circulating bone- and calcium-related factors (such as parathyroid hormone [PTH], bone-specific alkaline phosphatase [BSAP], and osteocalcin) are assessed in serum. Urine samples are analyzed for collagen crosslinks, including N-telopeptide, C-telopeptide, and deoxypyridinoline.

Calcium assessments are also conducted on blood and urine samples. Serum 1, 25 dihydroxyvitamin D is measured and serum 25 hydroxyvitamin D determined.

Endocrine factors that regulate and affect bone are also determined, to provide a complete profile of bone and calcium regulation and understand the effects of the countermeasures under consideration. These include testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), cortisol, estradiol, thyroxine (free T4), and thyroid stimulating hormone. These bone standard measures are summarized in Table A-8.

Table A-8. Bone Standard Measures

Measures of Bone Mineral Content (BMC) and Bone Mineral Density (BMD)	
DEXA	BMC, Areal BMD (whole body, regional lumbar spine and hip, calcaneus and forearm*), Body Composition
Blood/Serum Chemistry**	
Calcium Homeostasis	Total Calcium, Whole-blood Ionized Calcium
Gonadal Hormones	Testosterone, Estradiol
Calcitropic Hormones	25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, intact Parathyroid Hormone (PTH)
Endocrine Regulators	Thyroxine (Free T4), Thyroid Stimulating Hormone (hTSH III), Cortisol
Bone Turnover Markers (Bone Formation)	Osteocalcin, Bone Specific Alkaline Phosphatase (BSAP), N-terminal propeptide of type I procollagen (P1NP)
Urinary Measures	
Bone Turnover Markers (Bone Resorption)	N-telopeptide, C-telopeptide, Deoxypyridinoline
Minerals	Calcium

*Whole body, regional lumbar spine and hip are required measures. Calcaneus and forearm are recommended.

**Measures may overlap with the Nutrition/Hematology Discipline. When this is the case, measures are shared between disciplines.

Nutrition / Hematology Standard Measures

Nutritional assessment and general clinical chemistries provide an overview of subject health. These measures are summarized in Table A-9.

Table A-9. Required Nutrition / Hematology Standard Measures

Required Blood Measures	
Serum Chemistry	Carbon Dioxide, Blood Urea Nitrogen, Phosphorous, Magnesium, Bilirubin, Glutamyltransferase, Alkaline Phosphatase, Lactate Dehydrogenase, Creatine Kinase, Uric Acid, C Reactive Protein, Sodium, Potassium, Chloride, Creatinine, Aspartate Transaminase (AST), Alanine Transaminase (ALT), Cholesterol, Triglyceride, Glucose, Calcium
Whole Blood Analysis (CBC/differential/Platelets)	White Blood Count and differential, Red Blood Count, Hemoglobin, Mean Corpuscular Volume (MCV), Platelet Count, Reticulocyte Count Calculated values: Relative (Red Cell) Distributive Width (RDW), Hematocrit, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC)
Coagulation Test	Fibrinogen
Finger-Stick Tests (whole blood)	iCa, pH, PCO_2, PO_2 (optional tests, if included in analysis: Na, K, glucose, hematocrit) Calculated Values: TCO_2, HCO_3, BE, sO_2, Hgb
Hematologic and Iron Status Indicators	Transferrin Receptors, Transferrin, Ferritin, Ferritin Iron, RBC Folate, Iron, Total Iron Binding Capacity (TIBC) Calculated values: Ferritin Iron % Saturation, Transferrin Saturation

Required Blood Measures	
Ionized Calcium Profile	Whole-blood Ionized Calcium, pH-Whole-blood Calculated value: Ionized Calcium at pH 7.40
Hormones	Thyroxine (Free T4), Thyroid Stimulating Hormone (hTSH III), Testosterone, Estradiol, Dehydroepiandrosterone (DHEA), Dehydroepiandrosterone Sulfate (DHEA-S), Cortisol, Cytokines: TNF alpha, IL-6
Mineral Status	Zinc, Selenium, Iodine, Copper, Ceruloplasmin
Protein Status	Retinol Binding Protein, Transthyretin, Total Protein, Albumin
Nutritional Assessment (if blood volume allows)	
Water Soluble Vitamin Status	Erythrocyte Transketolase Stimulation, Erythrocyte Glutathione Reductase Activity, Erythrocyte nicotinamide adenosine dinucleotide and nicotinamide adenosine dinucleotide phosphate (NAD/NADP), Erythrocyte Transaminase Activity, Red Cell Folate, Folate, Homocysteine, Vitamin C, Pyridoxal 5-phosphate (PLP)
Fat Soluble Vitamin Status	Retinol, Retinyl palmitate, β-carotene, α –carotene, Serum Phylloquinone, α-tocopherol, γtocopherol, Tocopherol : lipid ratio, vitamin D binding protein and plasma heme, 25-hydroxyvitamin D

Required Urinary Measures	
Urinanalysis	Specific Gravity, pH, Color, Appearance, Protein, Glucose, Bilirubin, Urobilinogen, Ketone, Nitrite, Blood, Leukocyte Esterase, Total volume, pH, Creatinine
Minerals	Calcium, Phosphorus, Magnesium, Copper, Selenium, Zinc, Iodine
Protein Status	3-methyl histidine, Nitrogen
Renal Stone Risk	Sodium, Potassium, Uric Acid, Citrate, Oxalate, Sulfate, Suspersaturation of Brushite, Struvite and Calcium Oxalate
Nutritional Assessment (if blood volume allows for full blood testing complement, then the following urine tests shall be included as well)	
Water Soluble Vitamins	N-methyl nicotinamide, 2-pyridone, 4-pyridoxic acid
Other Measures	
Body Mass	Daily
DXA for body composition	Before and after bed rest
Dietary Intake	Daily

Immunology Standard Measures

The following list describes the required immune standard measures for bed rest studies:

- Complete blood count (CBC)
- Basic leukocyte subsets
- Stress hormone levels (saliva and or plasma measures)
- Plasma immunoglobulin G (IgG) levels
- Viral antibody levels
- Alpha 1 globulin, alpha 2 globulin, beta globulin, gamma globulin

Ocular Standard Measures

Intraocular Pressure

Intraocular pressure (IOP) is the fluid pressure of the aqueous humor inside the anterior chamber of the eye. Tonometry will be performed on the right and left eye using a commercial tonometer. In preparation for the measurement, 2 drops of topical anesthetic will be given in each eye to anesthetize the eye. The operator will stabilize the subject's head and gently tap the tonometer tip to the clear surface of the open eye directly over pupil to obtain the measurement.

Ocular Ultrasound

The thickness of the optic nerve and nerve sheath will be analyzed using Prosolv (Indianapolis, IN). Other parameters that will be derived from the ocular ultrasound scan include assessment of optic nerve tortuosity, and increased optic sheath-to-optic nerve diameter. The ultrasound scan will also be used to identify changes in globe morphology, including flattening of the posterior globe, globe axial measurements, and choroidal engorgement.

Optical Coherence Tomography and A-Scan
Optical coherence tomography (OCT) will be used to measure retinal thickness, volume, and retinal nerve fiber layer (RNFL) thickness using a method of quantitative cross sectional analysis. Axial samples of A-scans are obtained in each "scan pass“. When all of the A-scans are combined into one image, the image has a resolving power of about 10 microns vertically and 20 microns horizontally. Consequently, OCT has a high sensitivity for detecting subtle changes to the RNFL of the optic nerve head. An anterior segment module allows measurement of corneal thickness, anterior scleral thickness, and anterior chamber angles. Subjects are seated and place their chin on a chin rest while focusing their eyes into a machine. The machine performs a scan and the image and device generated report are viewed by the ophthalmologist or optometrist.
A minimal set of measures for OCT are listed below:
1. RNFL (circle)
2. Radial
3. Single Line
4. Macula
5. PMB (vertical block)
6. Disc block
7. Anterior segment parameters

Psychology Standard Measures

Positive and Negative Affect Scale (PANAS)
The PANAS is a 20-item self-evaluation questionnaire that measures affects, or indicators of emotional states. Emotional states are important to study during situations of isolation and confinement like bed rest experiments because they reflect the general state of the person at one step of the experiment. The PANAS separately assesses positive and negative affects. A positive affect reflects the extent to which a person feels enthusiastic, active and alert. Therefore, a person displaying high-positive affect has high energy, full concentration, and pleasurable engagement. Low-positive affect is characterized by sadness and lethargy. The separate measure of negative affect reflects the degree to which a person feels subjective distress and unpleasant engagement. A high-negative affect is described by anger, contempt, disgust, guilt, fear and nervousness. A low-negative affect describes a state of calmness and serenity.

General Health Questionnaire (GHQ)
GHQ is a self-evaluation questionnaire measuring the current mental state of the individual. GHQ-12 or GHQ-28 will be used for bed rest studies. GHQ-12 provides an overall total score for mental health. GHQ-28 provides an overall total score and scores on 4 subscales of somatic symptoms, anxiety, insomnia, social dysfunction and severe depression. The advantage of having these 4 subscales makes the GHQ-28 a useful measure for bed rest studies. Each item on the GHQ is rated on a 4-point scale (0 to 3) indicating ‘less than usual’, ‘no more than usual’, ‘rather more than usual’, and ‘much more than usual’.

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